

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
17 November 2005 (17.11.2005)

PCT

(10) International Publication Number
WO 2005/108382 A1

(51) International Patent Classification⁷: C07D 271/06,
413/06, 417/06, A61K 31/382, 31/397, 31/4025, 31/4245,
31/445, 31/541

(74) Common Representative: MERCK & CO., INC.; 126
East Lincoln Avenue, Rahway, New Jersey 07065-0907
(US).

(21) International Application Number:
PCT/US2005/015133

(22) International Filing Date: 29 April 2005 (29.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/568,034 4 May 2004 (04.05.2004) US

(71) Applicant (for all designated States except US): MERCK
& CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): XU, Jinyou
[CN/US]; 126 East Lincoln Avenue, Rahway, New Jer-
sey 07065-0907 (US). WEI, Lan [CA/US]; 126 East
Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).
MASTRACCHIO, Anthony [CA/US]; 126 East Lin-
coln Avenue, Rahway, New Jersey 07065-0907 (US).
EDMONDSON, Scott, D. [US/US]; 126 East Lincoln
Avenue, Rahway, New Jersey 07065-0907 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: 1,2,4-OXADIAZOLE DERIVATIVES AS DIPEPTIDYL PEPTIDASE-IV INHIBITORS FOR THE TREATMENT OR
PREVENTION OF DIABETES

(57) Abstract: The present invention is directed to novel 1,2,4-oxadiazole derivatives which are inhibitors of the dipeptidyl pep-
tidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl
peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical
compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such
diseases in which the dipeptidyl peptidase-IV enzyme is involved.



WO 2005/108382 A1

TITLE OF THE INVENTION

1,2,4-OXADIAZOLE DERIVATIVES AS DIPEPTIDYL PEPTIDASE-IV INHIBITORS FOR THE
TREATMENT OR PREVENTION OF DIABETES

5 FIELD OF THE INVENTION

The present invention relates to novel 1,2,4-oxadiazole derivatives which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising
10 these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

BACKGROUND OF THE INVENTION

Diabetes refers to a disease process derived from multiple causative factors and
15 characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type
20 2 diabetes mellitus are at especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutical control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In type 1 diabetes, or insulin-
25 dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In type 2 diabetes, or noninsulin dependent diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and adipose tissues, and the
30 plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and
35 secretion in the liver.

The available treatments for type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β -cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance due to the even higher plasma insulin levels can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of Type 2 diabetes.

The glitazones (i.e. 5-benzylthiazolidine-2,4-diones) are a more recently described class of compounds with potential for ameliorating many symptoms of type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of type 2 diabetes resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensitization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type II diabetes are agonists of the alpha, gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones (i.e., they are not thiazolidinediones). Serious side effects (e.g. liver toxicity) have occurred with some of the glitazones, such as troglitazone.

Additional methods of treating the disease are still under investigation. New biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (e.g. acarbose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

Compounds that are inhibitors of the dipeptidyl peptidase-IV ("DP-IV" or "DPP-IV") enzyme are also under investigation as drugs that may be useful in the treatment of diabetes, and particularly type 2 diabetes. See for example WO 97/40832, WO 98/19998, U.S. Patent No. 5,939,560, Bioorg. Med. Chem. Lett., 6: 1163-1166 (1996); and Bioorg. Med. Chem. Lett., 6: 2745-2748 (1996). The usefulness of DP-IV inhibitors in the treatment of type 2 diabetes is based on the fact that DP-IV *in vivo* readily inactivates glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and

GIP are incretins and are produced when food is consumed. The incretins stimulate production of insulin. Inhibition of DP-IV leads to decreased inactivation of the incretins, and this in turn results in increased effectiveness of the incretins in stimulating production of insulin by the pancreas. DP-IV inhibition therefore results in an increased level of serum insulin. Advantageously, since the incretins are produced by the body only when food is consumed, DP-IV inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to excessively low blood sugar (hypoglycemia). Inhibition of DP-IV is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is a dangerous side effect associated with the use of insulin secretagogues.

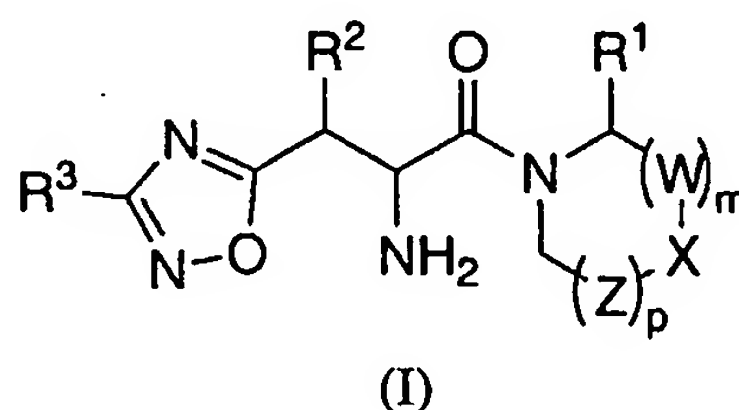
DP-IV inhibitors also have other therapeutic utilities, as discussed herein. DP-IV inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DP-IV inhibitors can be found for the treatment of diabetes and potentially other diseases and conditions. The therapeutic potential of DP-IV inhibitors for the treatment of type 2 diabetes is discussed by D.J. Drucker in *Exp. Opin. Invest. Drugs*, 12: 87-100 (2003) and by K. Augustyns, et al., in *Exp. Opin. Ther. Patents*, 13: 499-510 (2003).

SUMMARY OF THE INVENTION

The present invention is directed to novel 1,2,4-oxadiazole derivatives which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel 1,2,4-oxadiazole derivatives useful as inhibitors of dipeptidyl peptidase-IV. Compounds of the present invention are described by structural formula I:



or a pharmaceutically acceptable salt thereof; wherein

each n is independently 0, 1, or 2;

m and p are each independently 0 or 1;

X is CH₂, S, CHF, or CF₂;

W and Z are each independently CH₂, CHF, or CF₂;

R¹ is hydrogen or cyano;

5

R³ is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one to five R⁴ substituents;

R² is selected from the group consisting of

10

hydrogen,

C₁₋₁₀ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

C₂₋₁₀ alkenyl, wherein alkenyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

15

(CH₂)_n-aryl, wherein aryl is unsubstituted or substituted with one to five substituents

independently selected hydroxy, halogen, CO₂H, C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl,

and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

20

(CH₂)_n-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three

substituents independently selected from hydroxy, halogen, CO₂H, C₁₋₆

alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are

unsubstituted or substituted with one to five halogens,

25

(CH₂)_n-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three

substituents independently selected from oxo, hydroxy, halogen, CO₂H, C₁₋₆

alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are

unsubstituted or substituted with one to five halogens,

30

(CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three

substituents independently selected from halogen, hydroxy, CO₂H, C₁₋₆

alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are

unsubstituted or substituted with one to five halogens,

(CH₂)_nCOOH,

(CH₂)_nCOOC₁₋₆ alkyl,

35

(CH₂)_nCONR⁵R⁶, wherein R⁵ and R⁶ are independently selected from the group consisting of

hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl,

wherein alkyl is unsubstituted or substituted with one to five substituents independently

- selected from halogen and hydroxy and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;
- 5 or wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five
- 10 halogens; and
- wherein any methylene (CH₂) carbon atom in R² is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens;
- 15 each R⁴ is independently selected from the group consisting of
- halogen,
- cyano,
- hydroxy,
- C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,
- 20 C₁₋₆ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,
- (CH₂)_n-NR⁵R⁶,
- (CH₂)_n-CONR⁵R⁶,
- (CH₂)_n-OCONR⁵R⁶,
- (CH₂)_n-SO₂NR⁵R⁶,
- 25 (CH₂)_n-SO₂R⁸,
- (CH₂)_n-NR⁷SO₂R⁸,
- (CH₂)_n-NR⁷CONR⁵R⁶,
- (CH₂)_n-NR⁷COR⁷,
- (CH₂)_n-NR⁷CO₂R⁸,
- 30 (CH₂)_n-COOH,
- (CH₂)_n-COOC₁₋₆ alkyl,
- (CH₂)_n-aryl, wherein aryl is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, CO₂H,
- C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ alkoxy, wherein alkyl and
- 35 alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_n-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents independently selected from hydroxy, halogen, CO₂H, C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

5 (CH₂)_n-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, CO₂H, C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

10 (CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens, wherein any methylene (CH₂) carbon atom in R⁴ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens;

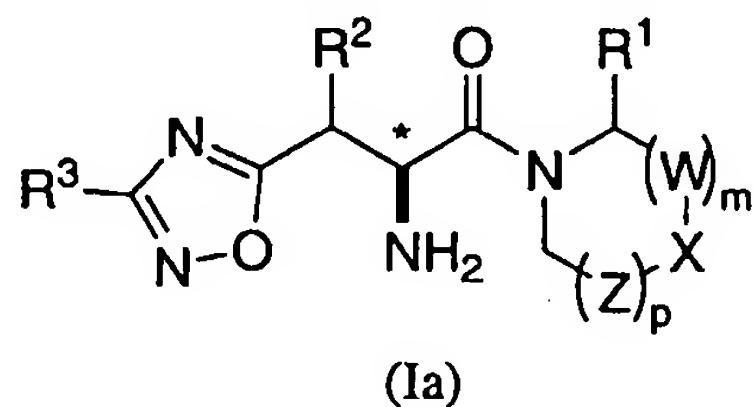
15 R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen and hydroxy and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from
20 halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to three substituents independently selected from halogen,
25 hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

each R⁸ is independently selected from the group consisting of tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five
30 halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens, and wherein any methylene (CH₂) carbon atom in R⁸ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to
35 five halogens; and

each R⁷ is hydrogen or R⁸.

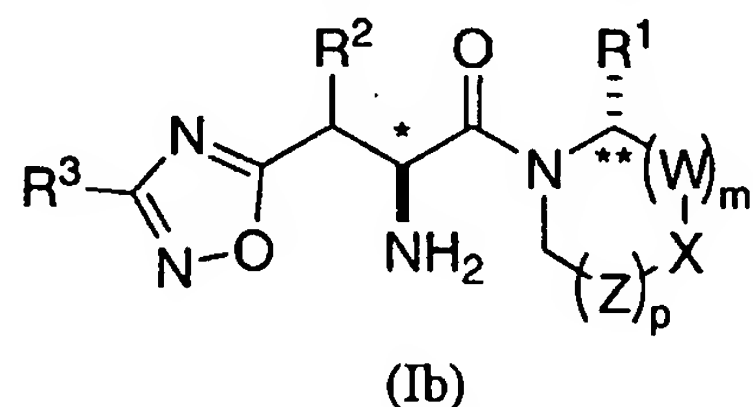
In one embodiment of the compounds of the present invention, the carbon atom marked with an * has the stereochemical configuration as depicted in formula Ia:



5

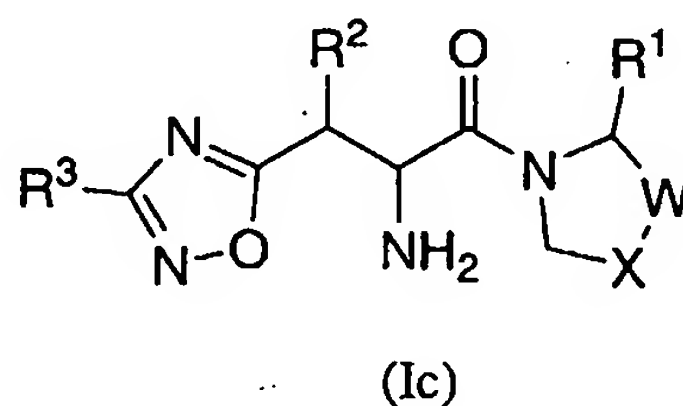
wherein W, X, Z, m, p, R¹, R², and R³ are as defined above.

In a class of this embodiment of the compounds of the present invention, the carbon atom attached to R¹ marked with an ** has the stereochemical configuration as depicted in the formula Ib:



10 wherein W, X, Z, m, p, R¹, R², and R³ are as defined above.

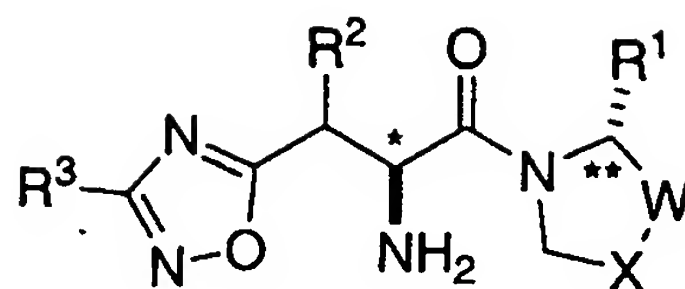
In a second embodiment of the compounds of the present invention, m is 1 and p is 0 as depicted in formula Ic:



wherein W, X, R¹, R², and R³ are as defined above.

15

A class of this embodiment encompasses compounds wherein the carbon atom marked with an * and the carbon atom marked with an ** have the stereochemical configurations as depicted in the formula Id:

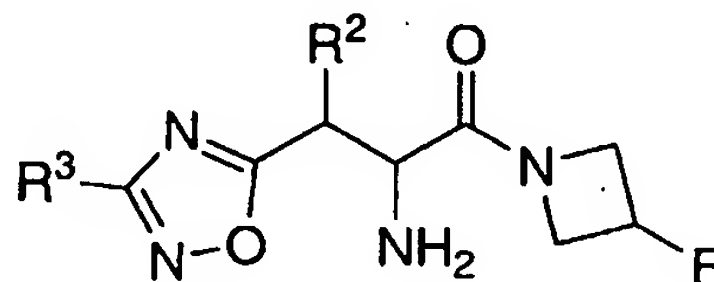


(Id)

wherein W, X, R¹, R², and R³ are as defined above.

In a subclass of this class of the compounds of the present invention, R¹ is hydrogen, W is CH₂, and X is S, CH₂, CHF, or CF₂.

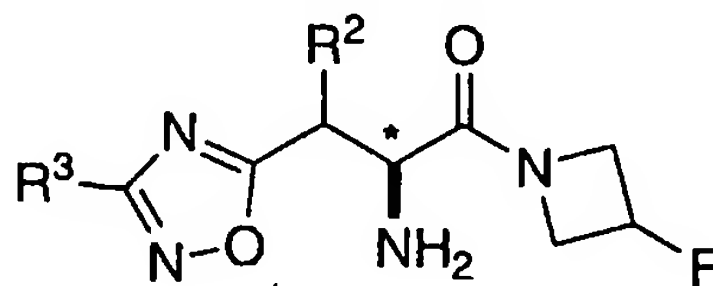
5 In a third embodiment of the compounds of the present invention, R¹ is hydrogen, X is CHF, and m and p are 0 as depicted in the formula Ie:



(Ie)

wherein R² and R³ are as defined above.

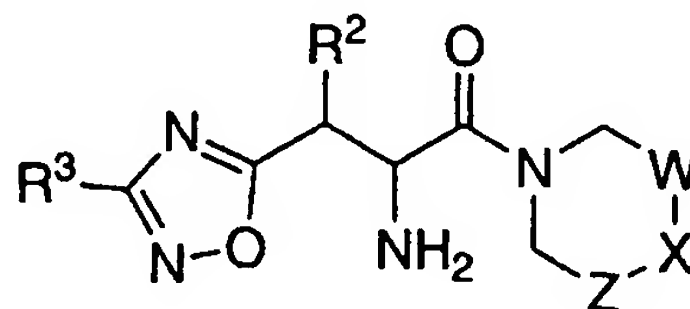
10 A class of this embodiment encompasses compounds wherein the carbon atom marked with an * has the stereochemical configuration as depicted in the formula If:



(If)

wherein R² and R³ are as defined above.

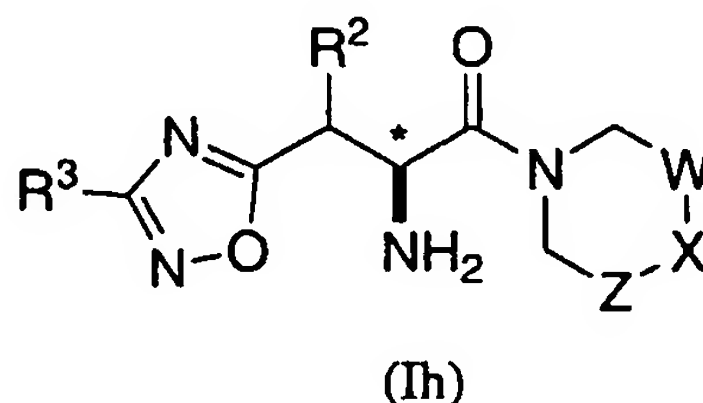
In a fourth embodiment of the compounds of the present invention, R¹ is hydrogen, and m and p are 1 as depicted in formula Ig:



(Ig)

wherein W, X, Z, R² and R³ are as defined above.

A class of this embodiment encompasses compounds wherein the carbon atom marked with an * has the stereochemical configuration as depicted in the formula 1h:



5 wherein W, X, Z, R², and R³ are as defined above.

In a subclass of this class, W and Z are CH₂ and X is CHF or CF₂.

In a fifth embodiment of the compounds of the present invention,

R² is selected from the group consisting of

C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents

10 independently selected from halogen or hydroxy,

C₂₋₆ alkenyl, wherein alkenyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

(CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, CO₂H, C₁₋₆

15 alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_nCOOH,

(CH₂)_nCOOC₁₋₆ alkyl,

20 (CH₂)_nCONR⁵R⁶, wherein R⁵ and R⁶ are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen and hydroxy and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

25 or wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

30

wherein any methylene (CH₂) carbon atom in R² is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens.

In a class of this embodiment of the compounds of the present invention, R² is selected from the group consisting of

C₁₋₃ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

CH₂-C₃₋₆ cycloalkyl,

COOH,

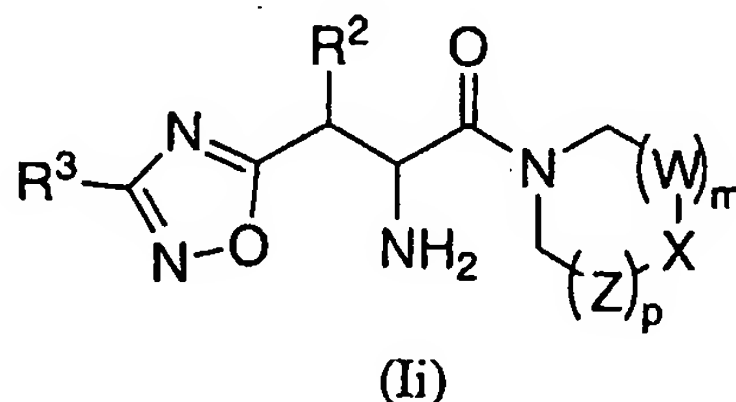
COOC₁₋₆ alkyl,

CONR⁵R⁶, wherein R⁵ and R⁶ are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen and hydroxy and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

or wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

A sixth embodiment of the present invention encompasses compounds of structural

formula Ii:



wherein X is CH₂, S, CHF, or CF₂;

W and Z are each independently CH₂, CHF, or CF₂;

R³ is aryl, unsubstituted or substituted with one to three R⁴ substituents;

R² is selected from the group consisting of:

methyl,

ethyl,
propyl,
2-methylpropyl,
propenyl,
5 CH₂-cyclopropyl,
CH₂-(1-methylcyclopropyl),
2-hydroxyethyl, and
2,2-difluoropropyl; and

each R⁴ is independently selected from the group consisting of:

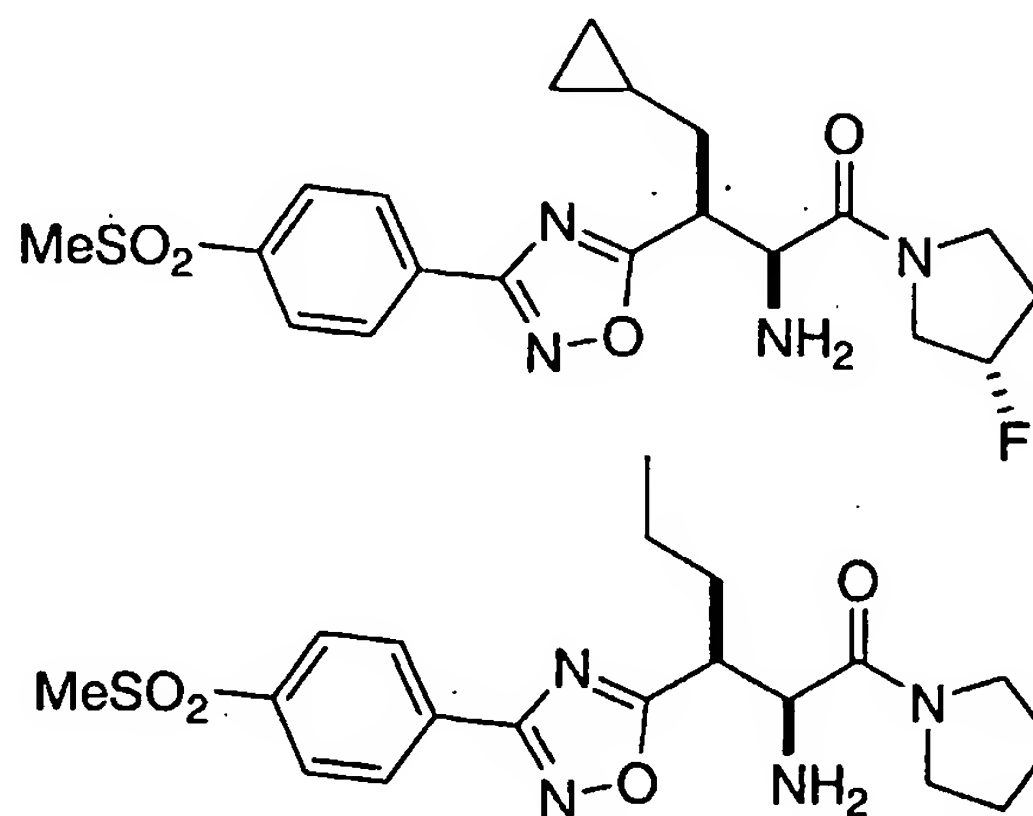
10 halogen,
C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,
C₁₋₆ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,
SO₂NR⁵R⁶,
SO₂R⁸,
15 NR⁷SO₂R⁸, and
heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents
independently selected from hydroxy, halogen, CO₂H,
C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are
unsubstituted or substituted with one to five halogens.

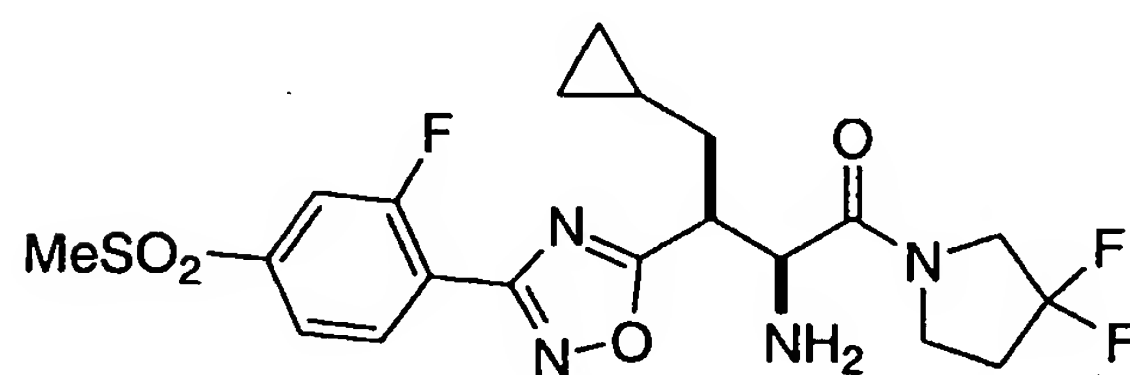
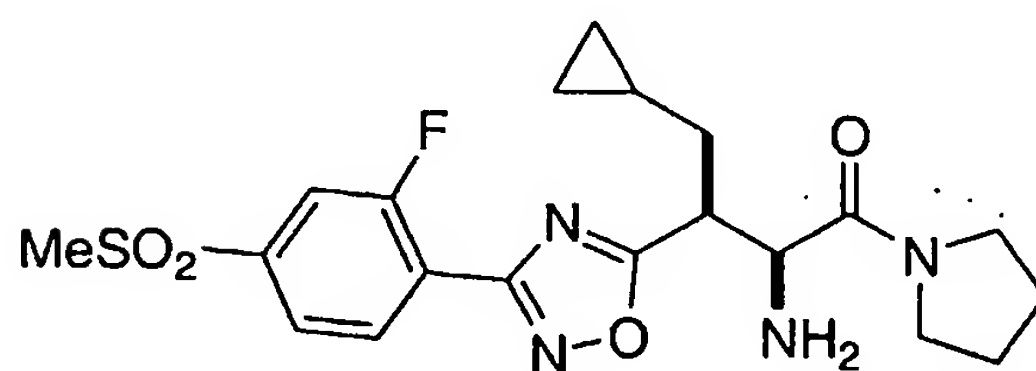
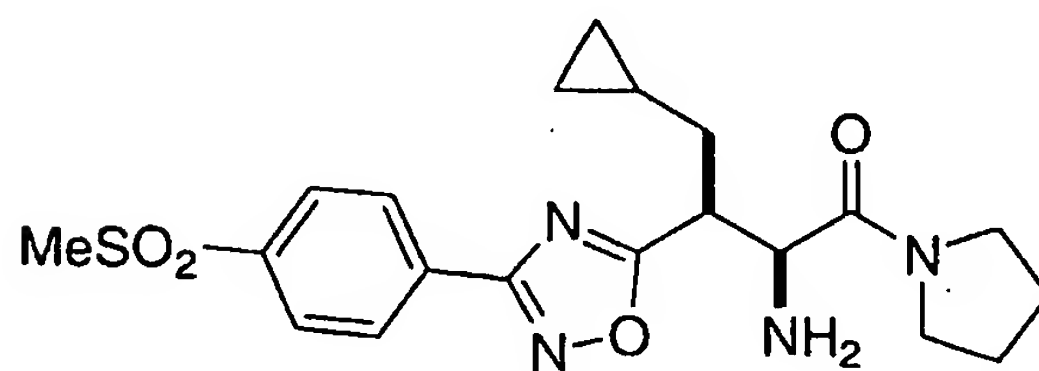
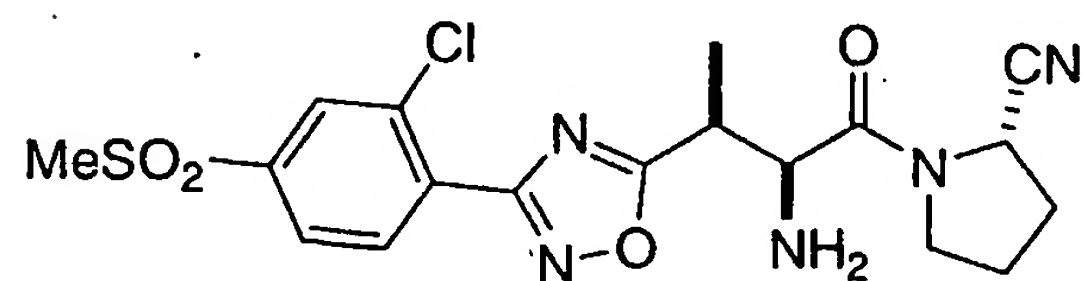
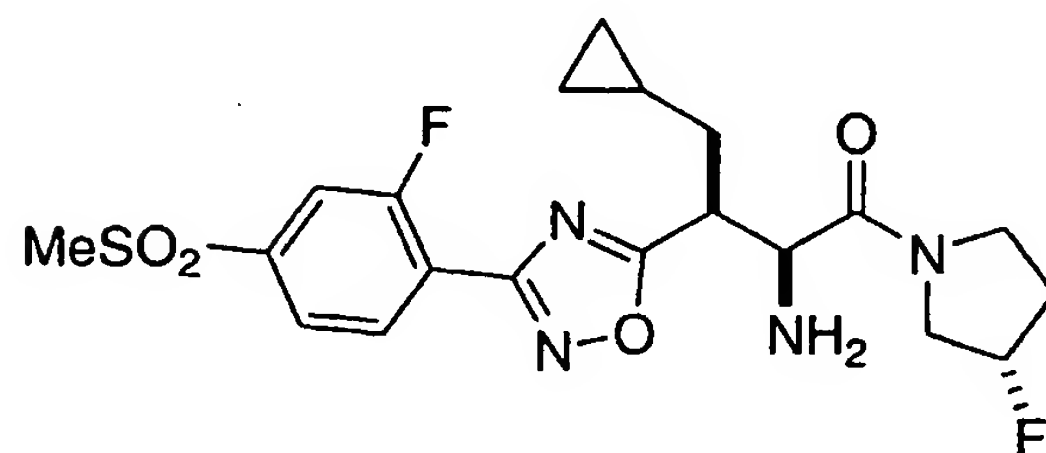
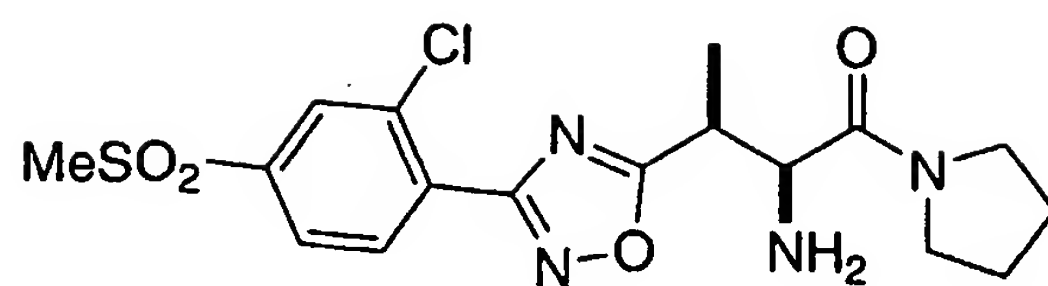
20 In a class of this embodiment, R³ is selected from the group consisting of:

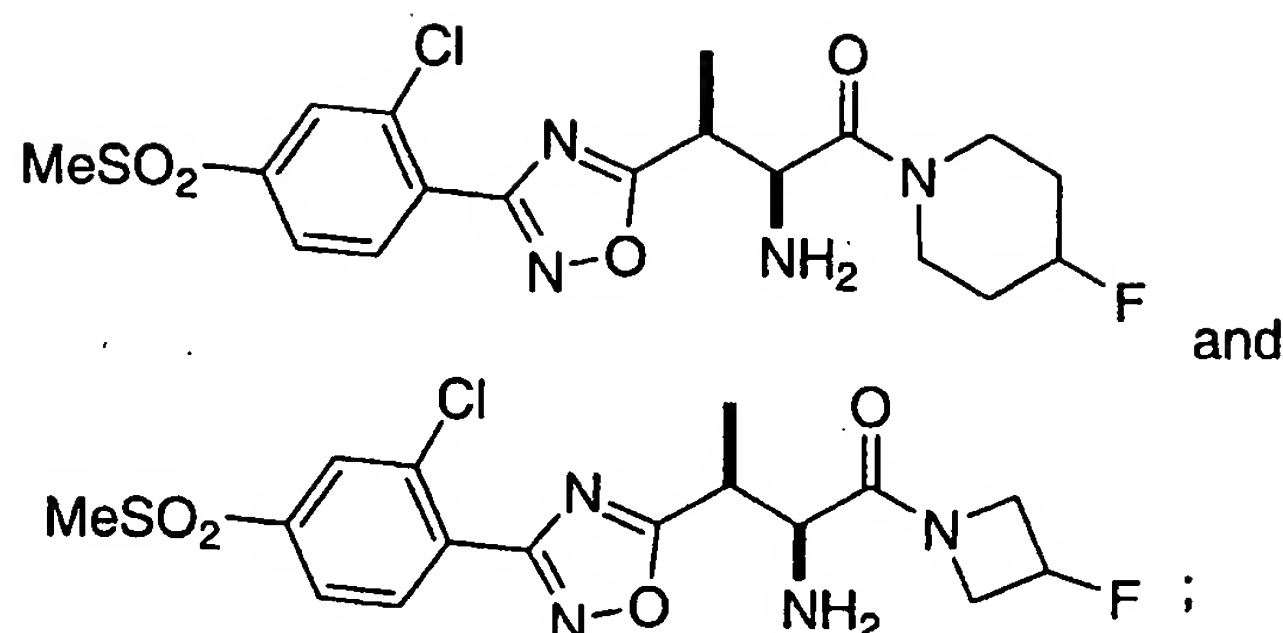
2-(trifluoromethoxy)phenyl,
4-(trifluoromethoxy)phenyl,
3,5-dichlorophenyl,
2,4-dichlorophenyl,
25 2,4-difluorophenyl,
3,5-difluorophenyl,
2-fluorophenyl,
4-fluorophenyl,
2-chlorophenyl,
30 4-chlorophenyl,
2-(trifluoromethyl)phenyl,
3-(trifluoromethyl)phenyl,
4-(trifluoromethyl)phenyl,
2-fluoro-4-(trifluoromethyl)phenyl,
35 2-chloro-4-(trifluoromethyl)phenyl,

- 2,6-dichloro-4-(trifluoromethyl)phenyl,
2-chloro-4-fluorophenyl,
2-chloro-4-bromophenyl,
4-(methylsulfonyl)phenyl,
5 4-[(trifluoromethyl)sulfonyl]phenyl,
4-(aminosulfonyl)phenyl,
4-[cyclopropylamino)sulfonyl]phenyl,
4-[(methylsulfonyl)amino]phenyl,
2-fluoro-4-(methylsulfonyl)phenyl,
10 2-chloro-4-(methylsulfonyl)phenyl,
2-fluoro-4-[(methylsulfonyl)amino]phenyl,
2-chloro-4-[(methylsulfonyl)amino]phenyl,
2-fluoro-4-(aminosulfonyl)phenyl,
2-chloro-4-(aminosulfonyl)phenyl,
15 2-chloro-4-(tetrazol-1-yl)phenyl, and
2-chloro-4-(tetrazol-5-yl)phenyl.

Illustrative, but nonlimiting, examples of compounds of the present invention that are useful as inhibitors of dipeptidyl peptidase-IV are the following:







or a pharmaceutically acceptable salt thereof.

As used herein the following definitions are applicable.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy and alkanoyl, means carbon chains which may be linear or branched, and combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like. Where the specified number of carbon atoms permits, e.g., from C₃-10, the term alkyl also includes cycloalkyl groups, and combinations of linear or branched alkyl chains combined with cycloalkyl structures. When no number of carbon atoms is specified, C₁-6 is intended.

"Cycloalkyl" is a subset of alkyl and means a saturated carbocyclic ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. A cycloalkyl group generally is monocyclic unless stated otherwise. Cycloalkyl groups are saturated unless otherwise defined.

The term "alkoxy" refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C₁-10 alkoxy), or any number within this range [i.e., methoxy (MeO-), ethoxy, isopropoxy, etc.].

The term "alkylthio" refers to straight or branched chain alkylsulfides of the number of carbon atoms specified (e.g., C₁-10 alkylthio), or any number within this range [i.e., methylthio (MeS-), ethylthio, isopropylthio, etc.].

The term "alkylamino" refers to straight or branched alkylamines of the number of carbon atoms specified (e.g., C₁-6 alkylamino), or any number within this range [i.e., methylamino, ethylamino, isopropylamino, t-butylamino, etc.].

The term "alkylsulfonyl" refers to straight or branched chain alkylsulfones of the number of carbon atoms specified (e.g., C₁-6 alkylsulfonyl), or any number within this range [i.e., methylsulfonyl (MeSO₂-), ethylsulfonyl, isopropylsulfonyl, etc.].

The term "alkyloxycarbonyl" refers to straight or branched chain esters of a carboxylic acid derivative of the present invention of the number of carbon atoms specified (e.g., C₁-6

alkyloxycarbonyl), or any number within this range [i.e., methyloxycarbonyl (MeOCO-), ethyloxycarbonyl, or butyloxycarbonyl].

"Aryl" means a mono- or polycyclic aromatic ring system containing carbon ring atoms. The preferred aryls are monocyclic or bicyclic 6-10 membered aromatic ring systems. Phenyl and naphthyl are preferred aryls. The most preferred aryl is phenyl.

"Heterocycle" and "heterocyclyl" refer to saturated or unsaturated non-aromatic rings or ring systems containing at least one heteroatom selected from O, S and N, further including the oxidized forms of sulfur, namely SO and SO₂. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, and the like.

"Heteroaryl" means an aromatic or partially aromatic heterocycle that contains at least one ring heteroatom selected from O, S and N. Heteroaryls also include heteroaryls fused to other kinds of rings, such as aryls, cycloalkyls and heterocycles that are not aromatic. Examples of heteroaryl groups include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridinyl, 2-oxo-(1*H*)-pyridinyl (2-hydroxy-pyridinyl), oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, triazinyl, thienyl, pyrimidinyl, pyrazinyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, dihydrobenzofuranyl, indolinyl, pyridazinyl, indazolyl, isoindolyl, dihydrobenzothienyl, indoliziny, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, carbazolyl, benzodioxolyl, quinoxalinyl, purinyl, furazanyl, isobenzylfuranyl, benzimidazolyl, benzofuranyl, benzothienyl, quinolyl, indolyl, isoquinolyl, dibenzofuranyl, imidazo[1,2-*a*]pyridinyl, [1,2,4-triazolo][4,3-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4-triazolo][1,5-*a*]pyridinyl, 2-oxo-1,3-benzoxazolyl, 4-oxo-3*H*-quinazolinyl, 3-oxo-[1,2,4]-triazolo[4,3-*a*]-2*H*-pyridinyl, 5-oxo-[1,2,4]-4*H*-oxadiazolyl, 2-oxo-[1,3,4]-3*H*-oxadiazolyl, 2-oxo-1,3-dihydro-2*H*-imidazolyl, 3-oxo-2,4-dihydro-3*H*-1,2,4-triazolyl, and the like. For heterocyclyl and heteroaryl groups, rings and ring systems containing from 3-15 atoms are included, forming 1-3 rings.

"Halogen" refers to fluorine, chlorine, bromine and iodine. Chlorine and fluorine are generally preferred. Fluorine is most preferred when the halogens are substituted on an alkyl or alkoxy group (e.g. CF₃O and CF₃CH₂O).

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. In particular the compounds of the present invention have an asymmetric center at the carbon atom marked with an * in formulae Ia, Ib, Id, If, and Ih and at the carbon atoms marked with an * and ** in formulae Ib and Id. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule, such as at the carbon atom to which the R²

substituent is attached. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

5 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

 Some of the compounds described herein may exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof
10 are encompassed with compounds of the present invention.

 Formula I shows the structure of the class of compounds without preferred stereochemistry. Formula Ia shows the preferred stereochemistry at the carbon atom to which is attached the amino group of the alpha-amino acid from which these compounds are prepared. Formula Ib shows the preferred stereochemistry at the carbon atom to which is attached the amino group of the alpha-amino
15 acid from which these compounds are prepared and at the stereogenic carbon atom to which the R¹ substituent is attached.

 The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or
20 crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

 If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a
25 diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which
30 methods are well known in the art.

 Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

 It will be understood that, as used herein, references to the compounds of structural
35 formula I are meant to also include the pharmaceutically acceptable salts, and also salts that are not

pharmaceutically acceptable when they are used as precursors to the free compounds or their pharmaceutically acceptable salts or in other synthetic manipulations.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present invention include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

Also, in the case of a carboxylic acid (-COOH) or alcohol group being present in the compounds of the present invention, pharmaceutically acceptable esters of carboxylic acid derivatives, such as methyl, ethyl, or pivaloyloxymethyl, or acyl derivatives of alcohols, such as acetate or maleate, can be employed. Included are those esters and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations.

Solvates, and in particular, the hydrates of the compounds of structural formula I are included in the present invention as well.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

The subject compounds are useful in a method of inhibiting the dipeptidyl peptidase-IV enzyme in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as inhibitors of dipeptidyl peptidase-IV enzyme activity.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

The present invention is further directed to a method for the manufacture of a medicament for inhibiting dipeptidyl peptidase-IV enzyme activity in humans and animals comprising combining a compound of the present invention with a pharmaceutically acceptable carrier or diluent. More particularly, the present invention is directed to the use of a compound of structural formula I in the manufacture of a medicament for use in treating a condition selected from the group consisting of hyperglycemia, Type 2 diabetes, obesity, and a lipid disorder in a mammal, wherein the lipid disorder is selected from the group consisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, and high LDL.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female, in whom inhibition of dipeptidyl peptidase-IV enzyme activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or

excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as inhibitors of dipeptidyl peptidase-IV enzyme activity may be demonstrated by methodology known in the art. Inhibition constants are determined as follows. A continuous fluorometric assay is employed with the substrate Gly-Pro-AMC, which is cleaved by DP-IV to release the fluorescent AMC leaving group. The kinetic parameters that describe this reaction are as follows: $K_m = 50 \mu\text{M}$; $k_{cat} = 75 \text{ s}^{-1}$; $k_{cat}/K_m = 1.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$. A typical reaction contains approximately 50 pM enzyme, 50 μM Gly-Pro-AMC, and buffer (100 mM HEPES, pH 7.5, 0.1 mg/ml BSA) in a total reaction volume of 100 μl . Liberation of AMC is monitored continuously in a 96-well plate fluorometer using an excitation wavelength of 360 nm and an emission wavelength of 460 nm. Under these conditions, approximately 0.8 μM AMC is produced in 30 minutes at 25 degrees C. The enzyme used in these studies was soluble (transmembrane domain and cytoplasmic extension excluded) human protein produced in a baculovirus expression system (Bac-To-Bac, Gibco BRL). The kinetic constants for hydrolysis of Gly-Pro-AMC and GLP-1 were found to be in accord with literature values for the native enzyme. To measure the dissociation constants for compounds, solutions of inhibitor in DMSO were added to reactions containing enzyme and substrate (final DMSO concentration is 1%). All experiments were conducted at room temperature using the standard reaction conditions described above. To determine the dissociation constants (K_i), reaction rates were fit by non-linear regression to the Michaelis-Menton equation for competitive inhibition. The errors in reproducing the dissociation constants are typically less than two-fold.

In particular, the compounds of the following examples had activity in inhibiting the dipeptidyl peptidase-IV enzyme in the aforementioned assays, generally with an IC_{50} of less than about 1 μM . Such a result is indicative of the intrinsic activity of the compounds in use as inhibitors the dipeptidyl peptidase-IV enzyme activity.

Dipeptidyl peptidase-IV enzyme (DP-IV) is a cell surface protein that has been implicated in a wide range of biological functions. It has a broad tissue distribution (intestine, kidney, liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, lymphoid and myeloid cells, serum), and distinct tissue and cell-type expression levels. DP-IV is identical to the T cell activation marker CD26, and it can cleave a number of immunoregulatory, endocrine, and neurological peptides *in vitro*. This has suggested a potential role for this peptidase in a variety of disease processes in humans or other species.

Accordingly, the subject compounds are useful in a method for the prevention or treatment of the following diseases, disorders and conditions.

Type II Diabetes and Related Disorders: It is well established that the incretins GLP-1 and GIP are rapidly inactivated *in vivo* by DP-IV. Studies with DP-IV^(-/-)-deficient mice and preliminary clinical trials indicate that DP-IV inhibition increases the steady state concentrations of GLP-1 and GIP, resulting in improved glucose tolerance. By analogy to GLP-1 and GIP, it is likely that other glucagon family peptides involved in glucose regulation are also inactivated by DP-IV (eg. PACAP). Inactivation of these peptides by DP-IV may also play a role in glucose homeostasis. The DP-IV inhibitors of the present invention therefore have utility in the treatment of type II diabetes and in the treatment and prevention of the numerous conditions that often accompany Type II diabetes, including Syndrome X (also known as Metabolic Syndrome), reactive hypoglycemia, and diabetic dyslipidemia. Obesity, discussed below, is another condition that is often found with Type II diabetes that may respond to treatment with the compounds of this invention.

The following diseases, disorders and conditions are related to Type 2 diabetes, and therefore may be treated, controlled or in some cases prevented, by treatment with the compounds of this invention: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component. In Syndrome X, also known as Metabolic Syndrome, obesity is thought to promote insulin resistance, diabetes, dyslipidemia, hypertension, and increased cardiovascular risk. Therefore, DP-IV inhibitors may also be useful to treat hypertension associated with this condition.

Obesity: DP-IV inhibitors may be useful for the treatment of obesity. This is based on the observed inhibitory effects on food intake and gastric emptying of GLP-1 and GLP-2. Exogenous administration of GLP-1 in humans significantly decreases food intake and slows gastric emptying (Am. J. Physiol., 277: R910-R916 (1999)). ICV administration of GLP-1 in rats and mice also has profound effects on food intake (Nature Medicine, 2: 1254-1258 (1996)). This inhibition of feeding is not observed in GLP-1R^(-/-) mice, indicating that these effects are mediated through brain GLP-1 receptors. By analogy to GLP-1, it is likely that GLP-2 is also regulated by DP-IV. ICV administration of GLP-2 also inhibits food intake, analogous to the effects observed with GLP-1 (Nature Medicine, 6: 802-807 (2000)). In addition, studies with DP-IV deficient mice suggest that these animals are resistant to diet-induced obesity and associated pathology (e.g. hyperinsulinonemia).

- Growth Hormone Deficiency: DP-IV inhibition may be useful for the treatment of growth hormone deficiency, based on the hypothesis that growth-hormone releasing factor (GRF), a peptide that stimulates release of growth hormone from the anterior pituitary, is cleaved by the DP-IV enzyme *in vivo* (WO 00/56297). The following data provide evidence that GRF is an endogenous substrate: (1) GRF is efficiently cleaved *in vitro* to generate the inactive product GRF[3-44] (BBA 1122: 147-153 (1992)); (2) GRF is rapidly degraded in plasma to GRF[3-44]; this is prevented by the DP-IV inhibitor diprotin A; and (3) GRF[3-44] is found in the plasma of a human GRF transgenic pig (J. Clin. Invest., 83: 1533-1540 (1989)). Thus DP-IV inhibitors may be useful for the same spectrum of indications which have been considered for growth hormone secretagogues.
- 10 Intestinal Injury: The potential for using DP-IV inhibitors for the treatment of intestinal injury is suggested by the results of studies indicating that glucagon-like peptide-2 (GLP-2), a likely endogenous substrate for DP-IV, may exhibit trophic effects on the intestinal epithelium (Regulatory Peptides, 90: 27-32 (2000)). Administration of GLP-2 results in increased small bowel mass in rodents and attenuates intestinal injury in rodent models of colitis and enteritis.
- 15 Immunosuppression: DP-IV inhibition may be useful for modulation of the immune response, based upon studies implicating the DP-IV enzyme in T cell activation and in chemokine processing, and efficacy of DP-IV inhibitors in *in vivo* models of disease. DP-IV has been shown to be identical to CD26, a cell surface marker for activated immune cells. The expression of CD26 is regulated by the differentiation and activation status of immune cells. It is generally accepted that CD26 functions as a
- 20 co-stimulatory molecule in *in vitro* models of T cell activation. A number of chemokines contain proline in the penultimate position, presumably to protect them from degradation by non-specific aminopeptidases. Many of these have been shown to be processed *in vitro* by DP-IV. In several cases (RANTES, LD78-beta, MDC, eotaxin, SDF-1alpha), cleavage results in an altered activity in chemotaxis and signaling assays. Receptor selectivity also appears to be modified in some cases (RANTES).
- 25 Multiple N-terminally truncated forms of a number of chemokines have been identified in *in vitro* cell culture systems, including the predicted products of DP-IV hydrolysis.

- DP-IV inhibitors have been shown to be efficacious immunosuppressants in animal models of transplantation and arthritis. Prodiptine (Pro-Pro-diphenyl-phosphonate), an irreversible inhibitor of DP-IV, was shown to double cardiac allograft survival in rats from day 7 to day 14
- 30 (Transplantation, 63: 1495-1500 (1997)). DP-IV inhibitors have been tested in collagen and alkyldiamine-induced arthritis in rats and showed a statistically significant attenuation of hind paw swelling in this model [Int. J. Immunopharmacology, 19:15-24 (1997) and Immunopharmacology, 40: 21-26 (1998)]. DP-IV is upregulated in a number of autoimmune diseases including rheumatoid arthritis, multiple sclerosis, Graves' disease, and Hashimoto's thyroiditis (Immunology Today, 20: 367-375
- 35 (1999)).

HIV Infection: DP-IV inhibition may be useful for the treatment or prevention of HIV infection or AIDS because a number of chemokines which inhibit HIV cell entry are potential substrates for DP-IV (Immunology Today 20: 367-375 (1999)). In the case of SDF-1alpha, cleavage decreases antiviral activity (PNAS, 95: 6331-6 (1998)). Thus, stabilization of SDF-1alpha through inhibition of DP-IV
5 would be expected to decrease HIV infectivity.

Hematopoiesis: DP-IV inhibition may be useful for the treatment or prevention of hematopoiesis because DP-IV may be involved in hematopoiesis. A DP-IV inhibitor, Val-Boro-Pro, stimulated hematopoiesis in a mouse model of cyclophosphamide-induced neutropenia (WO 99/56753).

Neuronal Disorders: DP-IV inhibition may be useful for the treatment or prevention of various neuronal
10 or psychiatric disorders because a number of peptides implicated in a variety of neuronal processes are cleaved *in vitro* by DP-IV. A DP-IV inhibitor thus may have a therapeutic benefit in the treatment of neuronal disorders. Endomorphin-2, beta-casomorphin, and substance P have all been shown to be *in vitro* substrates for DP-IV. In all cases, *in vitro* cleavage is highly efficient, with k_{cat}/K_m about $10^6 \text{ M}^{-1} \text{ s}^{-1}$ or greater. In an electric shock jump test model of analgesia in rats, a DP-IV inhibitor showed a
15 significant effect that was independent of the presence of exogenous endomorphin-2 (Brain Research, 815: 278-286 (1999)). Neuroprotective and neuroregenerative effects of DP-IV inhibitors were also evidenced by the inhibitors' ability to protect motor neurons from excitotoxic cell death, to protect striatal innervation of dopaminergic neurons when administered concurrently with MPTP, and to promote recovery of striatal innervation density when given in a therapeutic manner following MPTP
20 treatment [see Yong-Q. Wu, et al., "Neuroprotective Effects of Inhibitors of Dipeptidyl Peptidase-IV In Vitro and In Vivo," Int. Conf. On Dipeptidyl Aminopeptidases: Basic Science and Clinical Applications, September 26-29, 2002 (Berlin, Germany)].

Anxiety: Rats naturally deficient in DP-IV have an anxiolytic phenotype (WO 02/34243; Karl *et al.*, Physiol. Behav. 2003). DP-IV deficient mice also have an anxiolytic phenotype using the porsolt and
25 light/dark models. Thus DP-IV inhibitors may prove useful for treating anxiety and related disorders.

Memory and Cognition: GLP-1 agonists are active in models of learning (passive avoidance, Morris water maze) and neuronal injury (kainate-induced neuronal apoptosis) as demonstrated by Doring *et al.* (Nature Med. 9: 1173-1179 (2003)). The results suggest a physiological role for GLP-1 in learning and neuroprotection. Stabilization of GLP-1 by DP-IV inhibitors are expected to show similar effects

Tumor Invasion and Metastasis: DP-IV inhibition may be useful for the treatment or prevention of tumor
30 invasion and metastasis because an increase or decrease in expression of several ectopeptidases including DP-IV has been observed during the transformation of normal cells to a malignant phenotype (J. Exp. Med., 190: 301-305 (1999)). Up- or down-regulation of these proteins appears to be tissue and cell-type specific. For example, increased CD26/DP-IV expression has been observed on T cell lymphoma, T cell

acute lymphoblastic leukemia, cell-derived thyroid carcinomas, basal cell carcinomas, and breast carcinomas. Thus, DP-IV inhibitors may have utility in the treatment of such carcinomas.

Benign Prostatic Hypertrophy: DP-IV inhibition may be useful for the treatment of benign prostatic hypertrophy because increased DP-IV activity was noted in prostate tissue from patients with BPH (Eur. J. Clin. Chem. Clin. Biochem., 30: 333-338 (1992)).

Sperm motility/male contraception: DP-IV inhibition may be useful for the altering sperm motility and for male contraception because in seminal fluid, prostatesomes, prostate derived organelles important for sperm motility, possess very high levels of DP-IV activity (Eur. J. Clin. Chem. Clin. Biochem., 30: 333-338 (1992)).

Gingivitis: DP-IV inhibition may be useful for the treatment of gingivitis because DP-IV activity was found in gingival crevicular fluid and in some studies correlated with periodontal disease severity (Arch. Oral Biol., 37: 167-173 (1992)).

Osteoporosis: DP-IV inhibition may be useful for the treatment or prevention of osteoporosis because GIP receptors are present in osteoblasts.

The compounds of the present invention have utility in treating or preventing one or more of the following conditions or diseases: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) Type II diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis, (33) hypertension, (34) osteoporosis, and other conditions that may be treated or prevented by inhibition of DP-IV.

The subject compounds are further useful in a method for the prevention or treatment of the aforementioned diseases, disorders and conditions in combination with other agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, suppression or amelioration of diseases or conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy may also include therapies in which the

compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include
5 those that contain one or more other active ingredients, in addition to a compound of Formula I.

Examples of other active ingredients that may be administered in combination with a compound of Formula I, and either administered separately or in the same pharmaceutical composition, include, but are not limited to:

- (a) other dipeptidyl peptidase IV (DP-IV) inhibitors;
- 10 (b) insulin sensitizers including (i) PPAR γ agonists, such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, balaglitazone, and the like) and other PPAR ligands, including PPAR α/γ dual agonists, such as KRP-297 and muraglitazar, and PPAR α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (ii) biguanides such as metformin and phenformin, and (iii) protein tyrosine phosphatase-1B (PTP-1B)
15 inhibitors;
- (c) insulin or insulin mimetics;
- (d) sulfonylureas and other insulin secretagogues, such as tolbutamide, glyburide, glipizide, glimepiride, and meglitinides, such as nateglinide and repaglinide;
- (e) α -glucosidase inhibitors (such as acarbose and miglitol);
- 20 (f) glucagon receptor antagonists such as those disclosed in WO 98/04528, WO 99/01423, WO 00/39088, and WO 00/69810;
- (g) GLP-1, GLP-1 analogues or mimetics, and GLP-1 receptor agonists, such as exenatide-4 (exenatide), liraglutide (NN-2211), CJC-1131, LY-307161, and those disclosed in WO 00/42026 and WO 00/59887;
- 25 (h) GIP and GIP mimetics, such as those disclosed in WO 00/58360, and GIP receptor agonists;
- (i) PACAP, PACAP mimetics, and PACAP receptor agonists such as those disclosed in WO 01/23420;
- 30 (j) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, itavastatin, and rosuvastatin, and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinic alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (v) PPAR α/γ dual agonists, such as KRP-297 and muraglitazar, (vi) inhibitors of cholesterol absorption, such as beta-sitosterol and

ezetimibe, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as avasimibe, and (viii) anti-oxidants, such as probucol;

(k) PPAR δ agonists, such as those disclosed in WO 97/28149;

(l) antiobesity compounds, such as fenfluramine, dexfenfluramine, phentermine,
5 sibutramine, orlistat, neuropeptide Y₁ or Y₅ antagonists, CB1 receptor inverse agonists and antagonists, β_3 adrenergic receptor agonists, melanocortin-receptor agonists, in particular melanocortin-4 receptor agonists, ghrelin antagonists, bombesin receptor agonists (such as bombesin receptor subtype-3 agonists), and melanin-concentrating hormone (MCH) receptor antagonists;

(m) ileal bile acid transporter inhibitors;

10 (n) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, azulfidine, and selective cyclooxygenase-2 (COX-2) inhibitors;

(o) antihypertensive agents, such as ACE inhibitors (enalapril, lisinopril, captopril, quinapril, tandolapril), A-II receptor blockers (losartan, candesartan, irbesartan, valsartan, telmisartan,
15 and eprosartan), beta blockers and calcium channel blockers;

(p) glucokinase activators (GKAs);

(q) glucagon receptor antagonists;

(r) inhibitors of 11 β -hydroxysteroid dehydrogenase type 1; and

(s) inhibitors of cholesteryl ester transfer protein (CETP), such as torcetrapib.

20 Dipeptidyl peptidase-IV inhibitors that can be combined with compounds of structural formula I include those disclosed in WO 02/076450 (3 October 2002); WO 03/004498 (16 January 2003); WO 03/004496 (16 January 2003); EP 1 258 476 (20 November 2002); WO 02/083128 (24 October 2002); WO 02/062764 (15 August 2002); WO 03/000250 (3 January 2003); WO 03/002530 (9 January 2003); WO 03/002531 (9 January 2003); WO 03/002553 (9 January 2003); WO 03/002593 (9
25 January 2003); WO 03/000180 (3 January 2003); WO 03/082817 (9 October 2003); and WO 03/000181 (3 January 2003). Specific DP-IV inhibitor compounds include isoleucine thiazolidide (P32/98); NVP-DPP-728; and LAF 237.

Antiobesity compounds that can be combined with compounds of structural formula I include fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, neuropeptide Y₁ or Y₅
30 antagonists, cannabinoid CB1 receptor antagonists or inverse agonists, melanocortin receptor agonists, in particular, melanocortin-4 receptor agonists, ghrelin antagonists, bombesin receptor agonists, and melanin-concentrating hormone (MCH) receptor antagonists. For a review of anti-obesity compounds that can be combined with compounds of structural formula I, see S. Chaki et al., "Recent advances in feeding suppressing agents: potential therapeutic strategy for the treatment of obesity," Expert Opin. Ther. Patents, 11: 1677-1692 (2001); D. Spanswick and K. Lee, "Emerging antiobesity drugs," Expert
35

Opin. Emerging Drugs, 8: 217-237 (2003); and J.A. Fernandez-Lopez, et al., "Pharmacological Approaches for the Treatment of Obesity," Drugs, 62: 915-944 (2002).

Neuropeptide Y5 antagonists that can be combined with compounds of structural formula I include those disclosed in U.S. Patent No. 6,335,345 (1 January 2002) and WO 01/14376 (1 March 2001); and specific compounds identified as GW 59884A; GW 569180A; LY366377; and CGP-71683A.

Cannabinoid CB1 receptor antagonists that can be combined with compounds of formula I include those disclosed in PCT Publication WO 03/007887; U.S. Patent No. 5,624,941, such as rimonabant; PCT Publication WO 02/076949, such as SLV-319; U.S. Patent No. 6,028,084; PCT Publication WO 98/41519; PCT Publication WO 00/10968; PCT Publication WO 99/02499; U.S. Patent No. 5,532,237; and U.S. Patent No. 5,292,736.

Melanocortin receptor agonists that can be combined with compounds of structural formula I include those disclosed in WO 03/009847 (6 February 2003); WO 02/068388 (6 September 2002); WO 99/64002 (16 December 1999); WO 00/74679 (14 December 2000); WO 01/70708 (27 September 2001); and WO 01/70337 (27 September 2001) as well as those disclosed in J.D. Speake et al., "Recent advances in the development of melanocortin-4 receptor agonists," Expert Opin. Ther. Patents, 12: 1631-1638 (2002).

The potential utility of safe and effective activators of glucokinase (GKAs) for the treatment of diabetes is discussed in J. Grimsby et al., "Allosteric Activators of Glucokinase: Potential Role in Diabetes Therapy," Science, 301: 370-373 (2003).

When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g.,
5 intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses,
10 cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the
15 pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the
20 specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for
25 oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture
30 of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal
35 tract and thereby provide a sustained action over a longer period. For example, a time delay material

such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides,

for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

5 Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

10 The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or
15 diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa
20 butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

25 The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

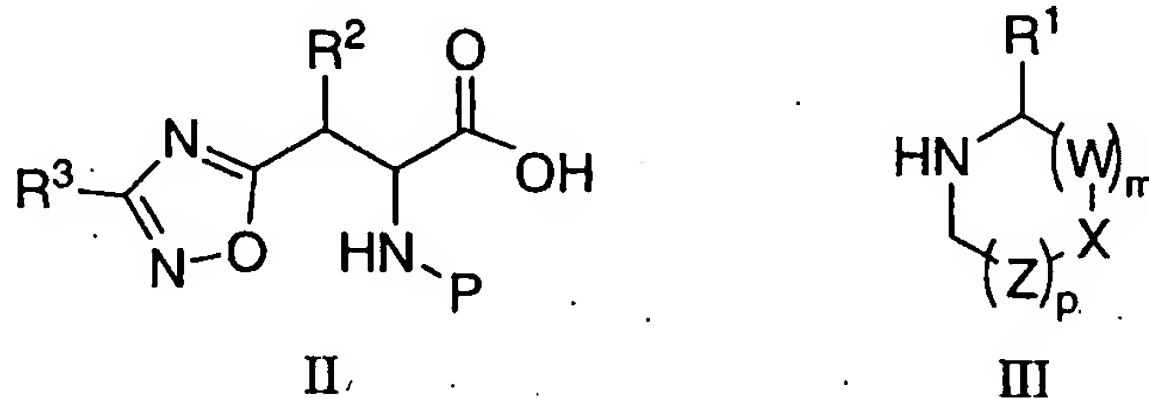
In the treatment or prevention of conditions which require inhibition of dipeptidyl peptidase-IV enzyme activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the
30 dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 mg of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0,
35 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 mg of

the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

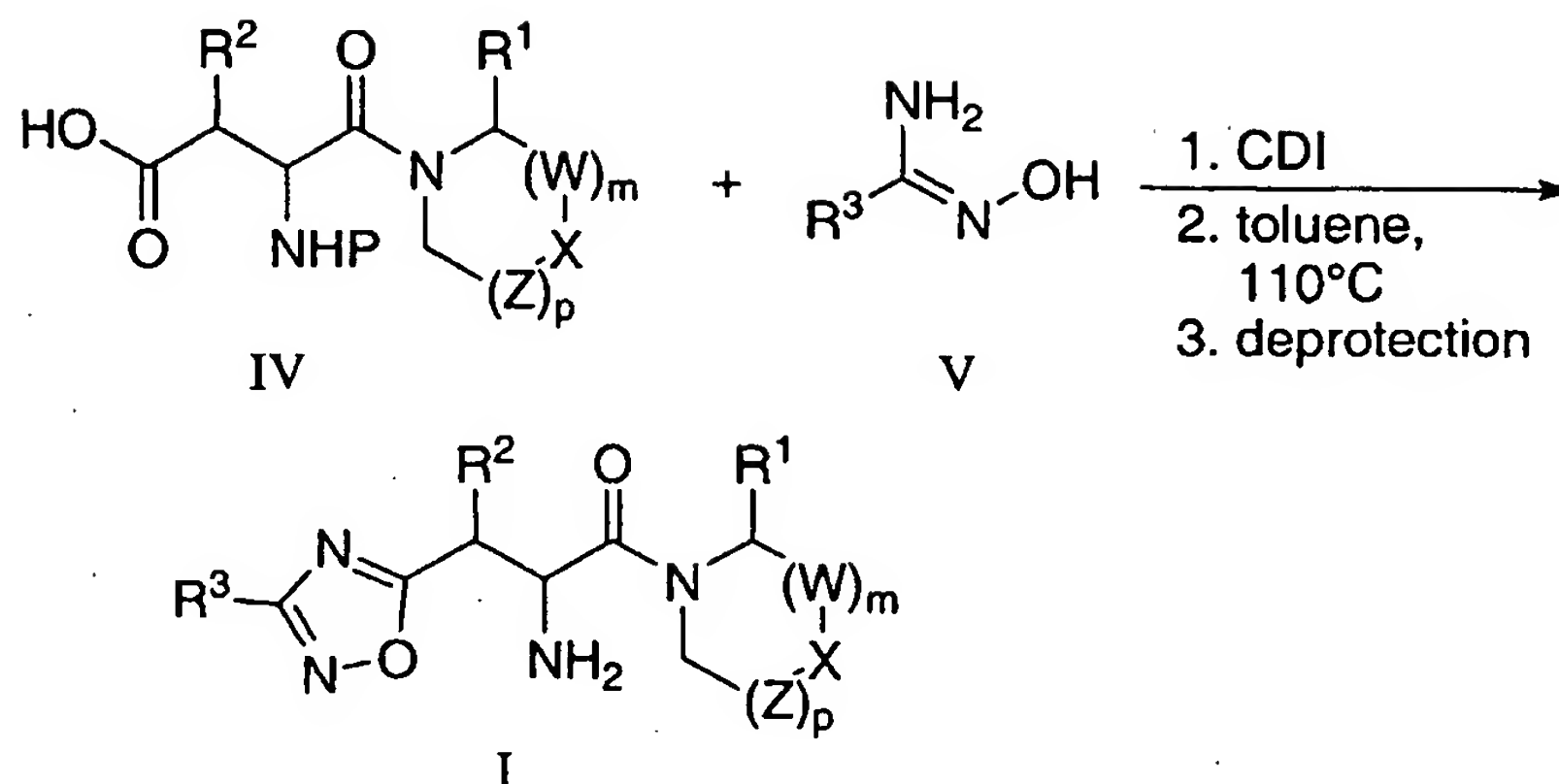
When treating or preventing diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 mg to about 100 mg per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 mg to about 1000 mg, preferably from about 1 mg to about 50 mg. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 mg to about 350 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The compounds of the present invention can be prepared from alpha- amino acid intermediates such as those of formula II and substituted heterocyclic intermediates such as those of formula III, using standard peptide coupling conditions followed by deprotection,



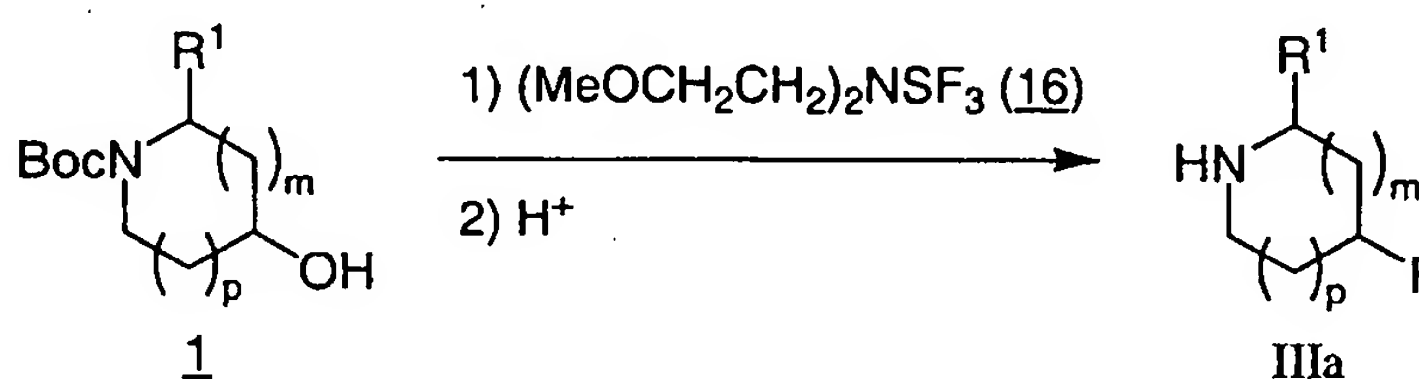
where m, p, W, X, Z, R¹, R², and R³ are as defined above and P is a suitable nitrogen protecting group such as tert-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), or 9-fluorenylmethoxycarbonyl (Fmoc). Alternatively, compounds of formula I can be prepared from intermediates, such as those of formula IV by activation of the carboxylic acid with standard peptide coupling reagents, such as *N,N*-carbonyldiimidazole, followed by condensation with an amidoxime V and cyclization under conditions familiar to those skilled in the art. Deprotection gives compounds of formula I.



Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

5

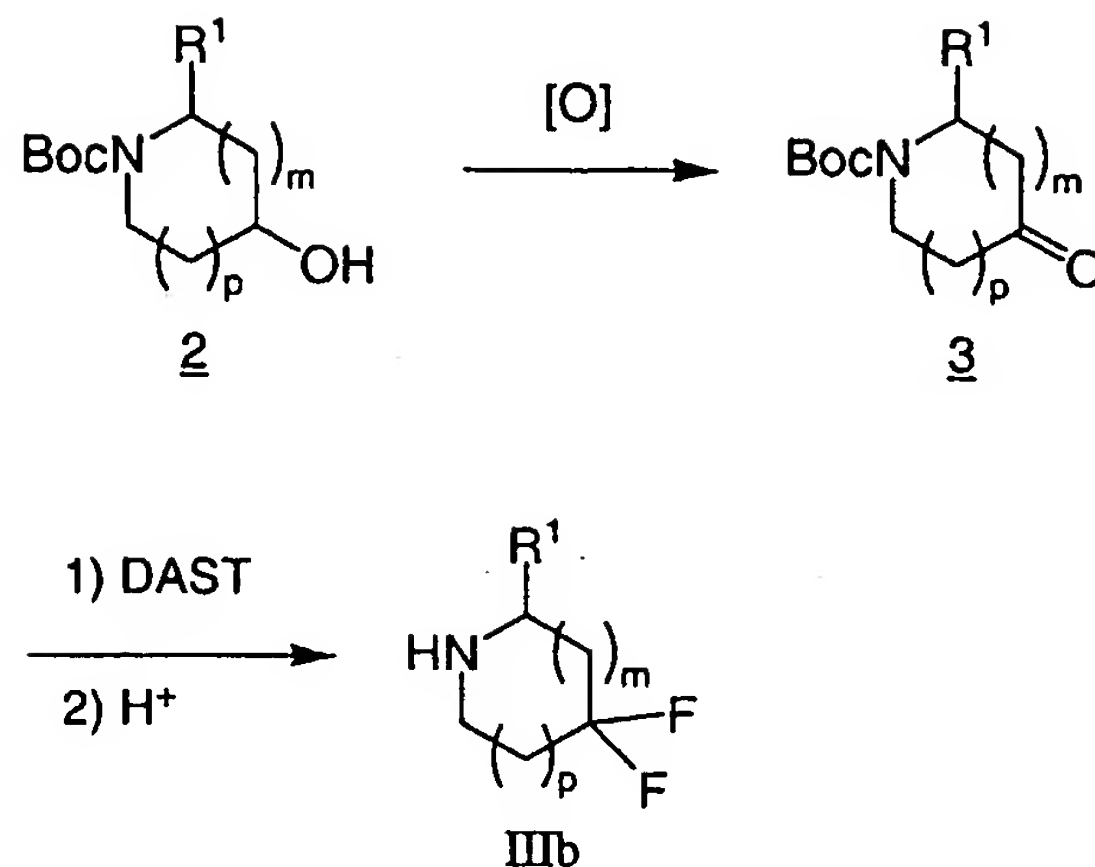
SCHEME 1



10

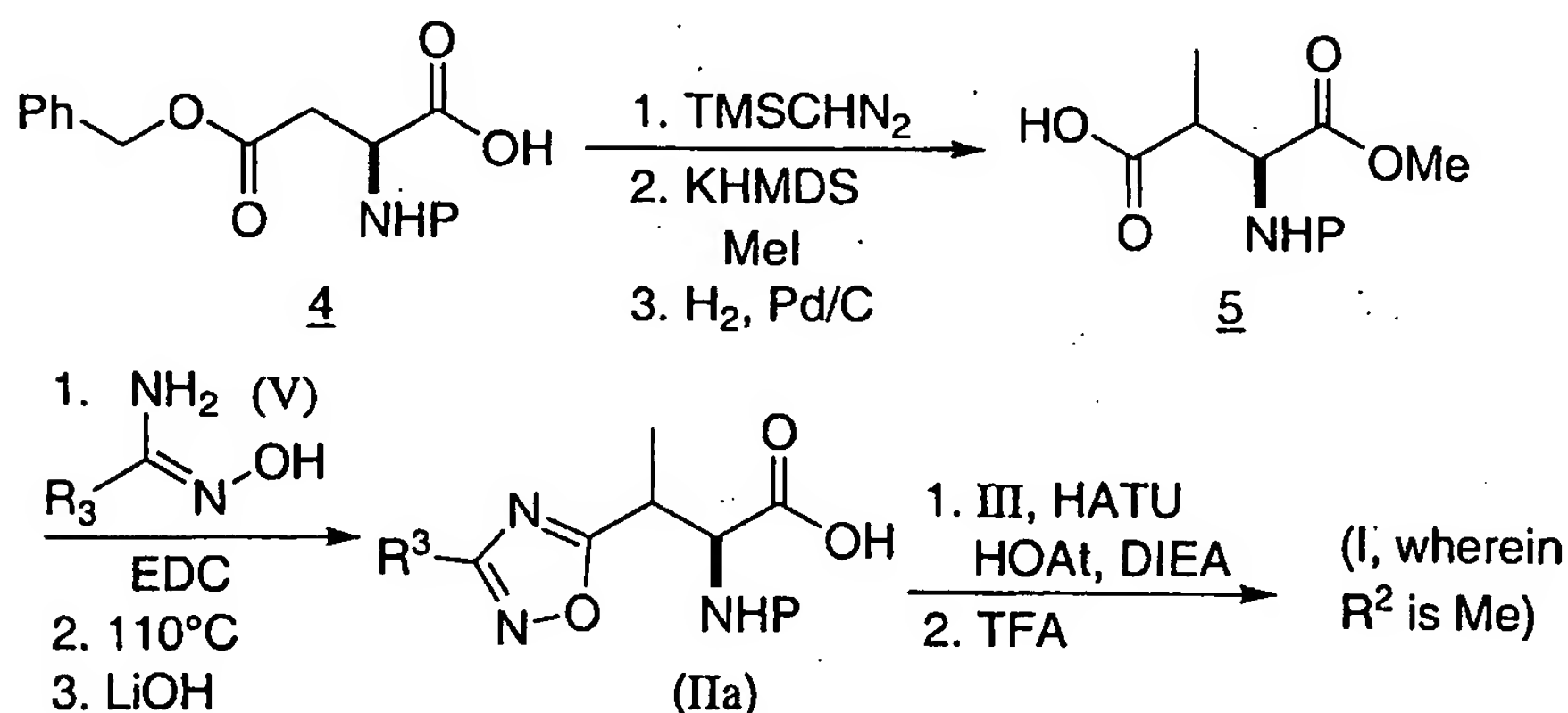
Compounds of formula III are commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One convenient method for the preparation of intermediate III wherein X is CHF and W and Z are CH₂ is shown in Scheme 1. An appropriately protected alcohol 1, which itself is known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art, is treated with a fluorinating reagent such as (diethylamino)sulfur trifluoride (DAST) or [bis(2-methoxyethyl)amino]sulfur trifluoride (16) to provide, after deprotection, the fluoro intermediate IIIa.

SCHEME 2



A method for the preparation of intermediate III wherein X is CF₂ and W and Z are CH₂ is shown in Scheme 2. An appropriately protected alcohol 2 is oxidized to the corresponding ketone 3 by a variety of methods known to those skilled in the art. Ketone 3 is treated with a fluorinating reagent, such as DAST, to provide, after deprotection, the difluoro intermediate IIIb.

SCHEME 3

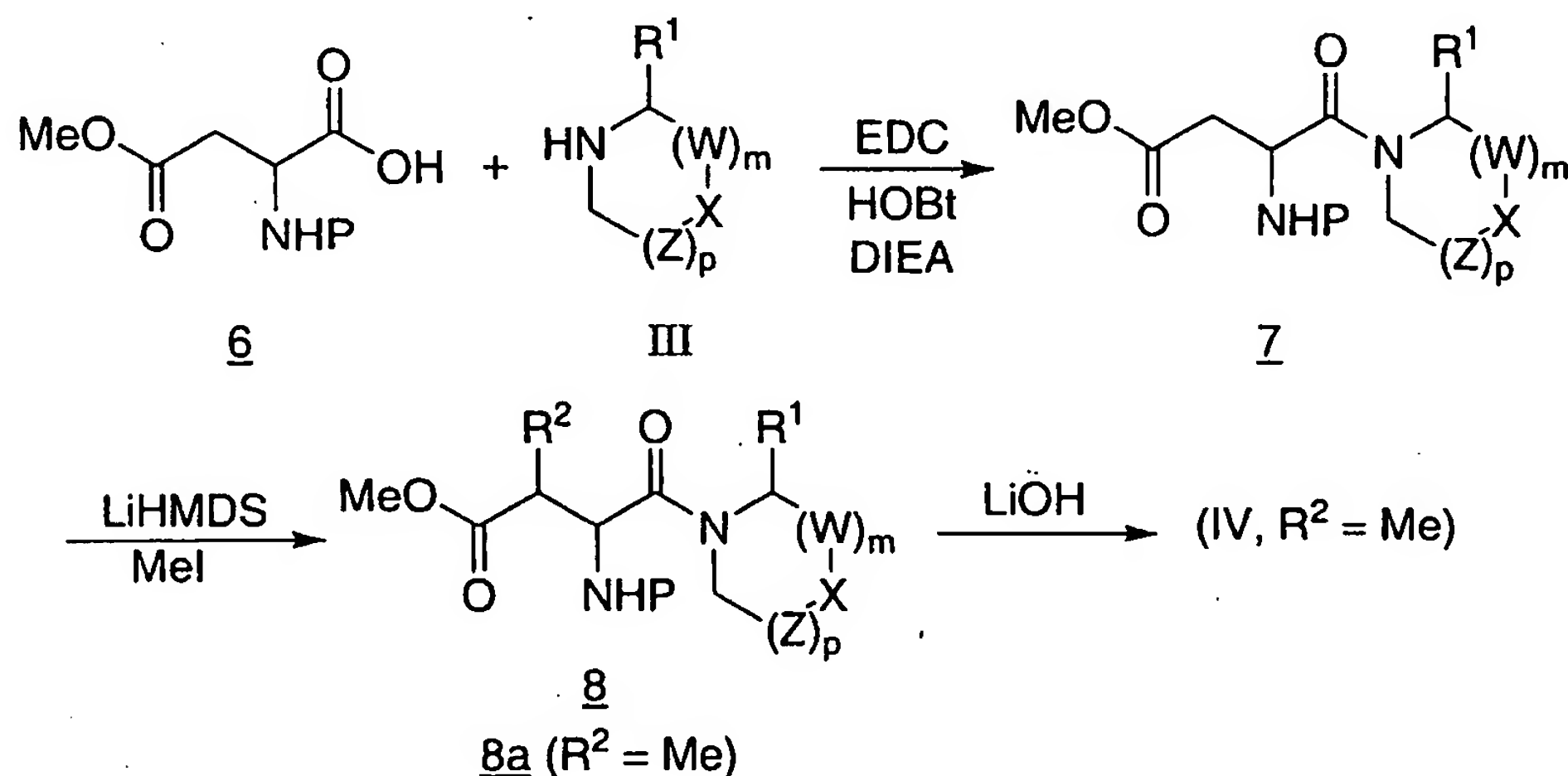


10

Compounds of formula II are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One such method is illustrated in Scheme 3. Starting with a commercially available aspartic acid derivative such as 4, esterification and subsequent alkylation with, for example, iodomethane affords the diester intermediate, which can be selectively

deprotected under hydrogenolytic conditions to afford intermediate 5. Coupling of an intermediate of formula 5 with amidoximes V, followed by cyclization under thermal conditions affords amidoxime intermediates, which may be saponified with, for example, lithium hydroxide to provide intermediates of structure II. Intermediates II and III are then coupled under standard peptide coupling conditions, for example, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 1-hydroxybenzotriazole (EDC/HOBT) or *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and 1-hydroxy-7-azabenzotriazole (HATU/HOAT) in a solvent such as *N,N*-dimethylformamide (DMF) or dichloromethane for 3 to 48 hours at ambient temperature to provide the *N*-protected amide intermediate. In some cases, Intermediate III may be a salt, such as a hydrochloride or trifluoroacetic acid salt, and in these cases it is convenient to add a base, generally *N,N*-diisopropylethylamine, to the coupling reaction. The protecting group is then removed with, for example, trifluoroacetic acid or methanolic hydrogen chloride in the case of Boc to give the desired amine I. The product is purified from unwanted side products, if necessary, by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel, such as with a Biotage® apparatus, or HPLC. Compounds that are purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.

SCHEME 4

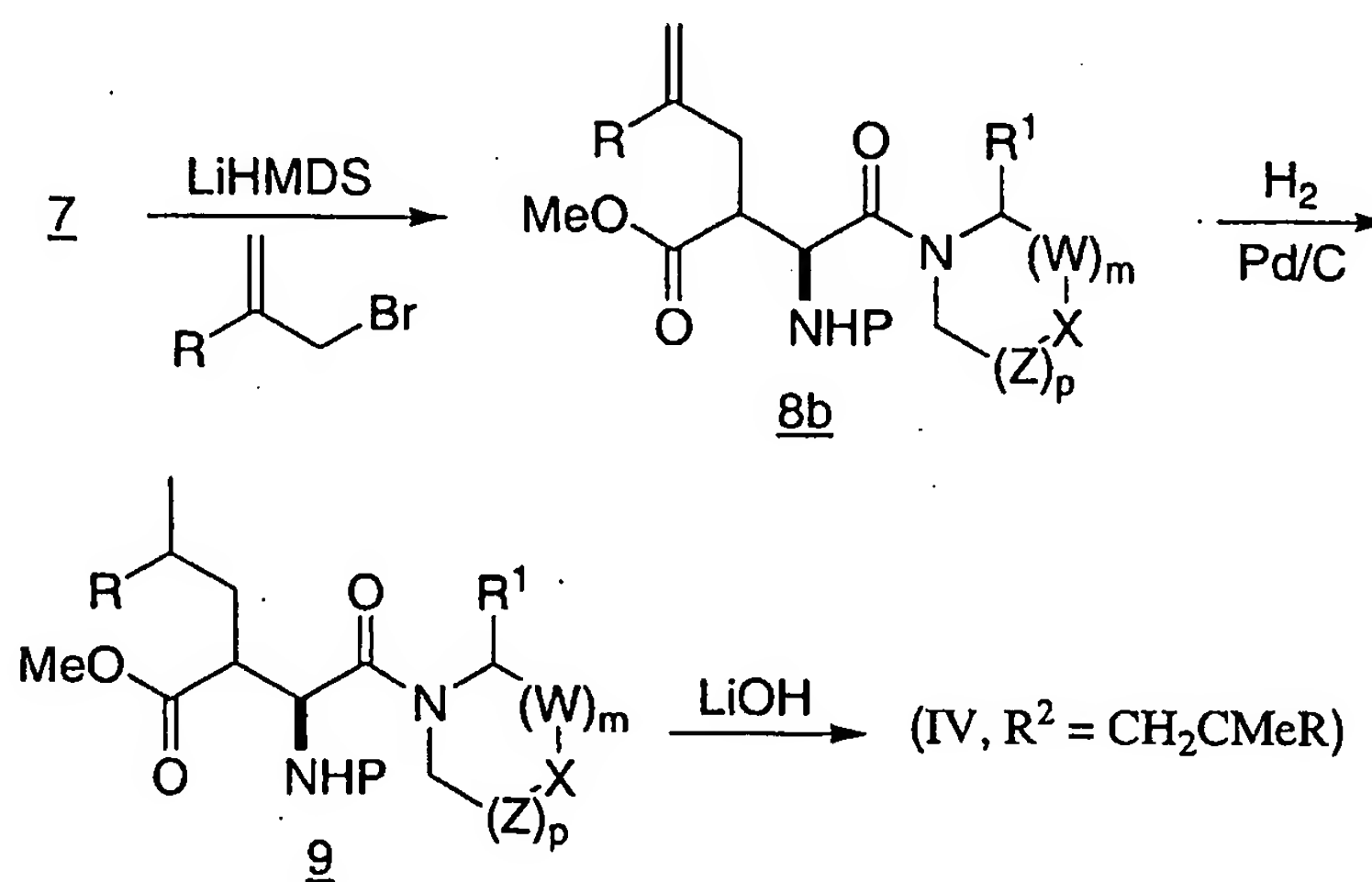


Compounds of the present invention may alternatively be prepared by reversing the order of introduction of the oxadiazole and tertiary amide functionalities, as illustrated in Scheme 4. Thus, commercially available *N*-protected aspartate derivatives such as 6 may be reacted with amines III using standard peptide coupling reagents such as, for example, *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) and 1-hydroxy-7-azabenzotriazole (HOAT), to form

amide intermediates such as 7. Subsequent treatment of the resulting intermediates of formula 7 with a strong base, such as the lithium or potassium salts of 1,1,1,3,3,3-hexamethyldisilazane (HMDS), followed by reaction with an alkyl halide, such as methyl iodide, affords intermediates of formula 8. Saponification of intermediates 8 with, for example, lithium hydroxide provides intermediates of formula IV.

In some cases the intermediates of formula 8 may be further modified, for example, by manipulation of the substituent R^2 , wherein R^2 contains an optionally substituted alkenyl group. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In one such example, intermediates of formula IV can be prepared by alkylation of intermediates of formula 7 with unsaturated alkyl halides such as, for example, allyl or methallyl bromide, to afford intermediates of structure 8b, as illustrated in Scheme 5. Catalytic hydrogenation provides intermediates of structure 9, which may be hydrolyzed with lithium hydroxide to form additional intermediates of formula IV.

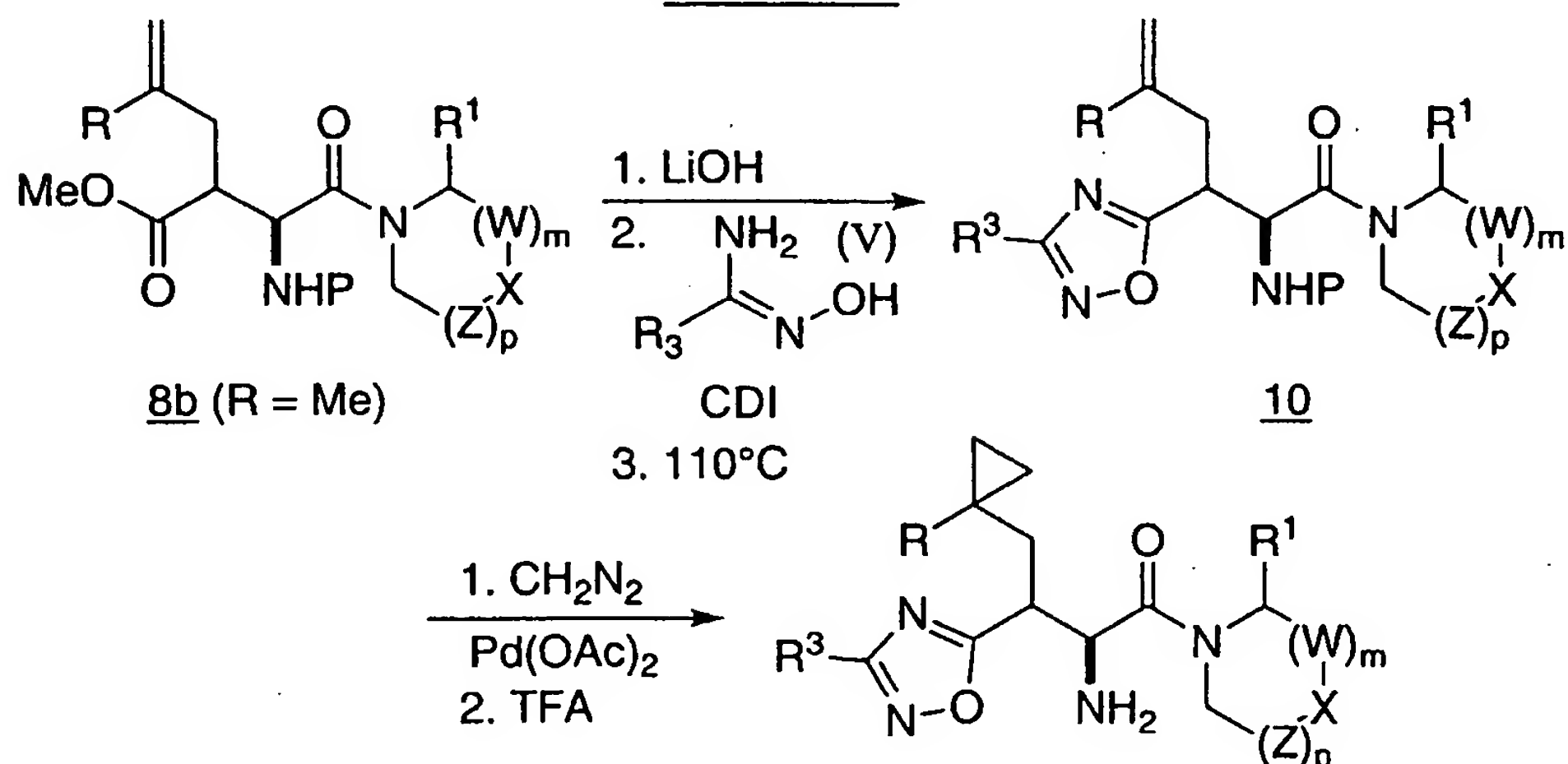
SCHEME 5



Compounds of formula I may alternatively be prepared from intermediates of formula 8 as illustrated in Scheme 6. Saponification of 8b with, for example, lithium hydroxide affords the corresponding carboxylic acid, which is coupled with an amidoxime of formula V and subsequently cyclized under thermal conditions to afford an oxadiazole intermediate of formula 10. Intermediate 10 may, in turn, be further elaborated by cyclopropanation of the alkenyl sidechain under conditions familiar to those skilled in the art, most conveniently using diazomethane and palladium(II) acetate. Deprotection

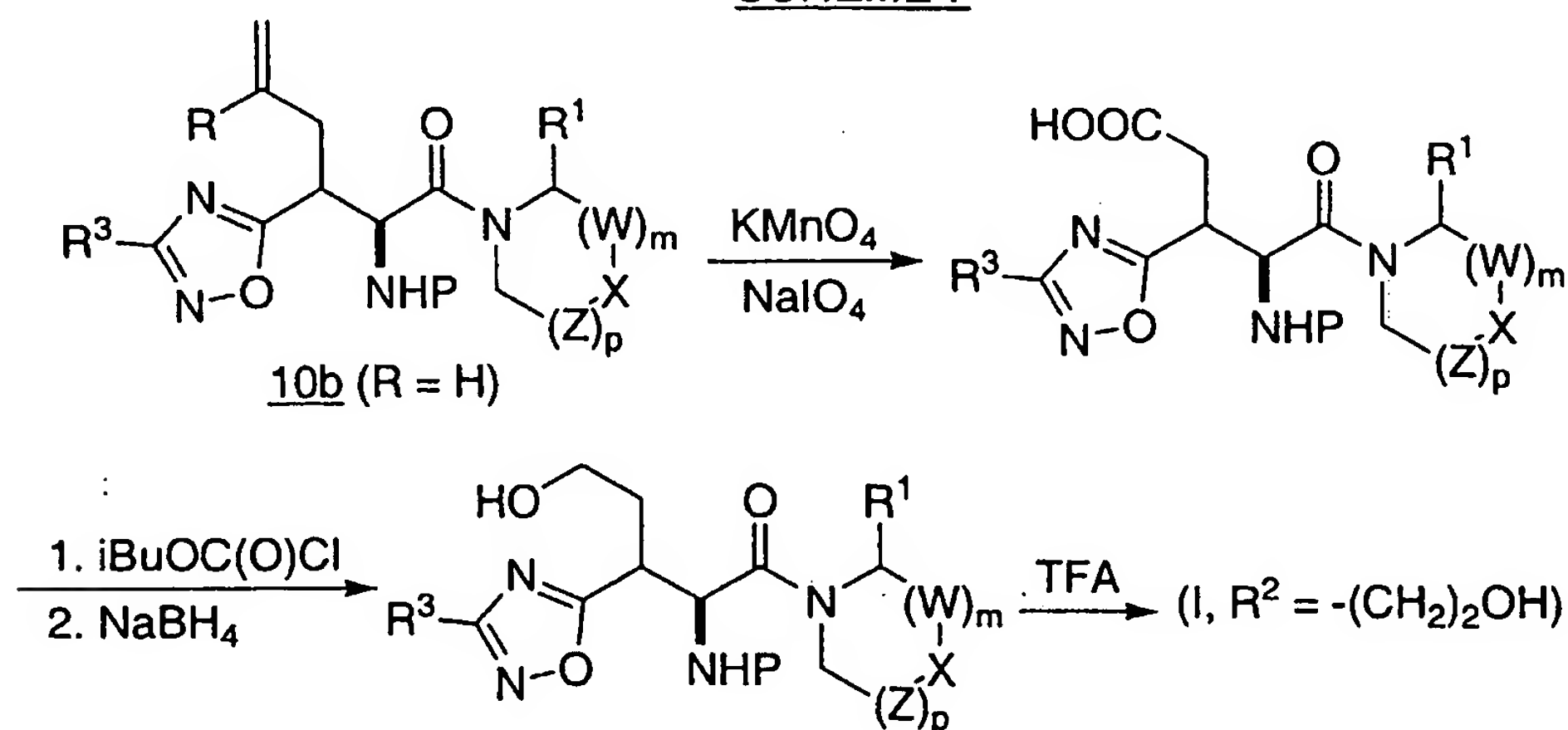
of the nitrogen protecting group affords additional examples of compounds of the present invention.

SCHEME 6

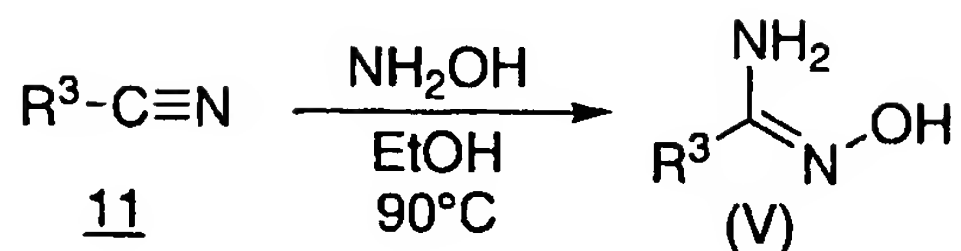


5 Compounds of the present invention that contain alternative substituents may also be prepared by the route illustrated in Scheme 7. Thus, oxidative cleavage of the alkenyl sidechain in intermediates of formula 10, wherein R is a hydrogen atom, followed by reduction

SCHEME 7



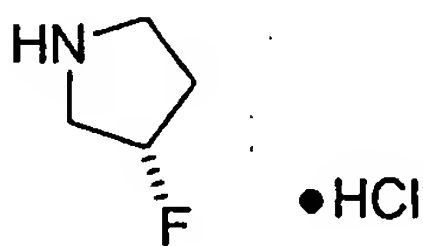
10 of the resulting carboxylic acid to the alcohol and subsequent deprotection, affords additional compounds of formula I.

SCHEME 8

The amidoximes V can be prepared by a number of routes familiar to those skilled in the art, most conveniently by reaction of a nitrile 11 with hydroxylamine in an alcoholic solvent such as methanol, ethanol or isopropanol for 3 to 48 hours at reflux temperature to provide the amidoxime intermediates V.

As will be readily apparent to those skilled in the art, since the aspartic acid-derived starting materials 4 and 6 are readily available in either enantiomeric form, the synthetic sequences described can be used to prepare compounds I in enantiomerically pure form. Additionally, since in some cases the alkylation of intermediates such as 4 and 7 may not be completely stereoselective, the synthetic sequences described above may afford mixtures of diastereomeric products, which can be conveniently separated, if necessary, by standard chromatographic methods familiar to those skilled in the art.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATE 1(3S)-3-Fluoropyrrolidine hydrochlorideStep A: Benzyl (3R)-3-hydroxypyrrolidine-1-carboxylate

A 22-L, 3-neck, round bottom flask equipped with mechanical stirrer, thermocouple, addition funnel and nitrogen bubbler was charged with 425 g (4.88 mol) of (3R)-3-hydroxypyrrolidine, 8 L of dichloromethane, and 1 L (7.17 mol) of triethylamine. The solution was cooled to 5 – 10 °C with an ice bath and then 1000 g (5.86 mol) of benzyl chloroformate was added dropwise over a period of about 1.5 h keeping the reaction temperature <20 °C. The reaction mixture was stirred for an additional hour in the ice bath, then the bath was removed and the reaction mixture was allowed to warm to ambient temperature overnight. The mixture was poured into a large extractor containing ~15 L of saturated

aqueous sodium bicarbonate solution. The aqueous phase was back-extracted with two 2-L portions of dichloromethane. The combined organics were dried over magnesium sulfate and concentrated to give an orange oil. The crude material was taken up in dichloromethane, applied to a 5-kg column of silica gel prepacked in 50% ethyl acetate/hexane, and eluted sequentially with 8 L of 50%, 16 L of 75%, then
5 100% ethyl acetate/hexane to provide the title compound as a yellow oil which crystallized upon standing.

Step B: Benzyl (3*S*)-3-fluoropyrrolidine-1-carboxylate

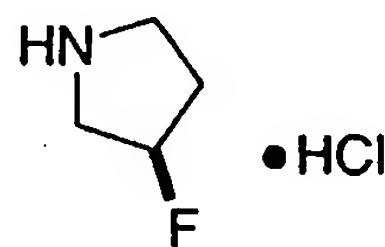
A 5-L, 3-neck, round bottom flask equipped with mechanical stirrer, thermocouple, addition funnel and nitrogen bubbler was charged with 375 mL (2.84 mol) of (diethylamino)sulfur
10 trifluoride and 400 mL of dichloromethane. The solution was cooled to -78°C . To this was added via addition funnel a solution of 304 g (1.37 mol) of benzyl (3*R*)-3-hydroxypyrrolidine-1-carboxylate in 400 mL of dichloromethane over a 2-h period keeping the reaction temperature $< -70^{\circ}\text{C}$. The reaction mixture was allowed to stir and warm slowly to ambient temperature overnight. The reaction mixture was added portion-wise with caution to a large extractor containing ice, water, and saturated aqueous
15 sodium bicarbonate solution. The mixture was extracted with 8 L of ethyl acetate. The organic layer was washed with saturated aqueous brine, dried over magnesium sulfate, and concentrated to give a brown oil. Purification by flash chromatography (silica gel, eluting with a 10 to 30% ethyl acetate/hexane gradient) gave the title compound as a brown oil.

Step C: (3*S*)-3-Fluoropyrrolidine hydrochloride salt

20 Benzyl (3*S*)-3-fluoropyrrolidine-1-carboxylate (249 g, 1.11 mmol) was dissolved in 2.3 L of ethanol and then 115 mL of water was added, followed by 30 g of 10% palladium on carbon. The mixture was shaken under 40 psi hydrogen for about 24 h. An additional 10 g and then 5 g of catalyst were added. The mixture was stirred under 40 psi hydrogen until complete. The mixture was filtered and the filter cake washed with ethanol. The combined filtrate and washings were treated with 185 mL
25 of concentrated hydrochloric acid and concentrated to a colorless oil. The residue was azeotroped with toluene, then 2 L of diethyl ether was added. Isopropyl alcohol was added until the the oil crystallized. The mixture was allowed to age at ambient temperature over the weekend. The crystals were collected, washed with diethyl ether, and dried in vacuo to give the title compound. $[\alpha]_{\text{D}} = +8.64$ ($c = 4$, methanol).

30

INTERMEDIATE 2



(3*R*)-3-Fluoropyrrolidine hydrochloride

Step A: Benzyl (3S)-3-acetoxypyrrolidine-1-carboxylate

A 22-L, 3 neck round bottom flask equipped with a mechanical stirrer, thermocouple, addition funnel and nitrogen bubbler was charged with 422 g (1.91 mol) of benzyl (3R)-3-hydroxypyrrolidine-1-carboxylate (Intermediate 1, Step A), 12 L of toluene, 751 g (2.86 mol) of triphenylphosphine, and 164 mL (2.86 mol) of glacial acetic acid. The resultant mixture was stirred at ambient temperature and then 500 g (2.87 mol) of diethyl azodicarboxylate was added via the addition funnel over a period of about 30 min, keeping the internal temperature <28 °C with a cold water bath. The reaction was stirred at ambient temperature overnight. The solvent was removed in vacuo and the residue was triturated with 6 L of diethyl ether. The solid was filtered off and washed well with diethyl ether. The filtrate and ether washings were combined and concentrated to a thick yellow oil with solids. Purification by flash chromatography (silica gel, eluting sequentially with 5% and a gradient of 10% to 30% ethyl acetate/hexane) gave the title compound as a pale yellow oil.

Step B: Benzyl (3S)-3-hydroxypyrrolidine-1-carboxylate

To a 20-L, three neck round bottom flask containing 427 g (1.62 mol) of benzyl (3S)-3-acetoxypyrrolidine-1-carboxylate was added 4 L of absolute ethanol followed by 101 g (1.57 mol) of potassium hydroxide in about 400 mL of water. After about 15 min, the reaction mixture was poured into 8 L of water and extracted with 8 L of ethyl acetate. The aqueous layer was then extracted with an additional 4 L of ethyl acetate. The combined organics were washed with saturated aqueous brine, dried over magnesium sulfate and concentrated to a thick oil and solids.

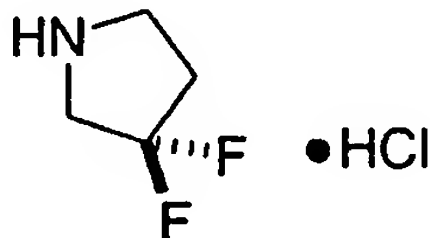
Step C: Benzyl (3R)-3-fluoropyrrolidine-1-carboxylate

A 366 g (1.62 mol) portion of benzyl (3S)-3-hydroxypyrrolidine-1-carboxylate was converted to the title compound essentially following the procedure outlined in Intermediate 1, Step B.

Step D: (3R)-3-Fluoropyrrolidine hydrochloride salt

A 222 g (1.0 mol) portion of benzyl (3R)-3-fluoropyrrolidine-1-carboxylate was converted to the title compound essentially following the procedure outlined in Intermediate 1, Step C; $[\alpha]_D = -8.61$ ($c = 4$, methanol).

INTERMEDIATE 3



3,3-Difluoropyrrolidine hydrochloride

Step A: Benzyl 3-oxopyrrolidine-1-carboxylate

A 12-L, 3 neck round bottom flask equipped with a mechanical stirrer, thermocouple, condenser, and nitrogen bubbler was charged with 351 g (1.61 mol) of benzyl (3*R*)-3-hydroxypyrrolidine-1-carboxylate (Intermediate 1, Step A), 6 L of dichloromethane, 500 g of powdered molecular sieves, and 400 g (3.41 mol) of *N*-methylmorpholine-*N*-oxide. The resultant suspension was stirred at ambient temperature and to this was added 12.9 g (0.0367 mol) of tetrapropylammonium perruthenate. The reaction temperature was kept at ≤ 30 °C with a cold water bath. The mixture was stirred at ambient temperature for 2 h. The mixture was poured onto a plug of 5 kg of silica gel and eluted with 10% ethyl acetate/dichloromethane to give the title compound as an orange oil.

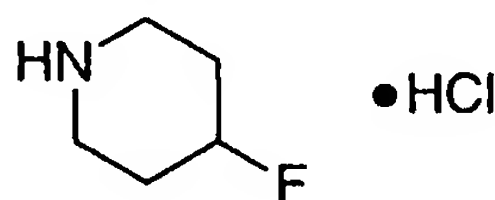
Step B: Benzyl 3,3-difluoropyrrolidine-1-carboxylate

A 12-L, 3 neck round bottom flask equipped with a mechanical stirrer, thermocouple, addition funnel and nitrogen bubbler was charged with 292 g (1.33 mol) of benzyl 3-oxopyrrolidine-1-carboxylate and 3 L of dichloromethane. To the stirring solution at ambient temperature was added dropwise 530 mL (4.0 mol) of (diethylamino)sulfur trifluoride over a period of about 3 h, keeping the internal temperature less than 25 °C using a cold water bath. The mixture was stirred at ambient temperature overnight. The mixture was poured into a large extractor containing ice and solid sodium bicarbonate. Eight liters of ethyl acetate were then added and the mixture was made basic with sodium bicarbonate. The organic layer was dried over magnesium sulfate and concentrated to 309 g of a brown oil. Purification by flash chromatography (silica gel, 10 to 20% ethyl acetate/hexane gradient) gave the title compound.

Step C: 3,3-Difluoropyrrolidine hydrochloride

A 242 g (1.00 mol) portion of benzyl 3,3-difluoropyrrolidine-1-carboxylate was converted to the title compound essentially following the procedure outlined in Intermediate 1, Step C. ^1H NMR (500 MHz, CD_3OD): δ 3.7 (t, 2H), 3.6 (t, 2H), 2.55 (m, 2H).

INTERMEDIATE 4



4-Fluoropiperidine hydrochloride

Step A: Benzyl 4-fluoro-1-piperidinecarboxylate

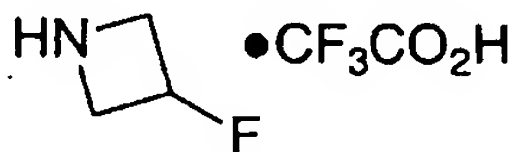
A 1-L, round bottom flask was charged with 12.64 g (51.4 mmol) of benzyl 4-oxo-1-piperidinecarboxylate and 300 mL of dichloromethane. To the stirring solution at -78 °C was added 19 mL (102.8 mmol) of [bis(2-methoxyethyl)amino]sulfur trifluoride via addition funnel over a period of about 1 h. The reaction mixture was allowed to warm slowly to ambient temperature overnight. The

reaction mixture was added portionwise with caution to a large extractor containing water and saturated aqueous sodium bicarbonate solution. The mixture was extracted with dichloromethane (3 x 300 mL). The combined organic layers were washed once with saturated aqueous sodium bicarbonate solution, twice with 10% aqueous hydrochloric acid solution and saturated aqueous brine, dried over sodium sulfate, and concentrated *in vacuo*. Purification by flash chromatography on a Biotage® system (gradient, hexane to 65% ethyl acetate/hexane) afforded the desired product. LC/MS 242.1 (M+1).

Step B: 4-Fluoropiperidine hydrochloride

Benzyl 4-fluoro-1-piperidinecarboxylate (5.5 g, 23.2 mmol) was dissolved in 80 mL of ethanol and 1.0 g of 20 % palladium hydroxide (dry basis) on carbon was added to the mixture. The mixture was shaken under 40 psi hydrogen for about 12 h then filtered through a celite pad and washed with 100 mL of methanol. The combined filtrate and washings were treated with 60 mL of 1 M hydrochloric acid in diethyl ether and concentrated to a white waxy solid. The solid was dried *in vacuo* to give the title compound as a solid. The material was used without further purification. ¹H NMR (CDCl₃): δ 4.95 (d, J = 47.4 Hz, 1 H), 3.70 (br s, 1 H), 3.34-3.27 (m, 4 H), 2.29 (dt, J = 37.1, 12.3 Hz, 2 H), 2.16 (br s, 2 H).

INTERMEDIATE 5



3-Fluoroazetidine trifluoroacetic acid salt

Step A: 1-Benzhydryl-3-fluoroazetidine

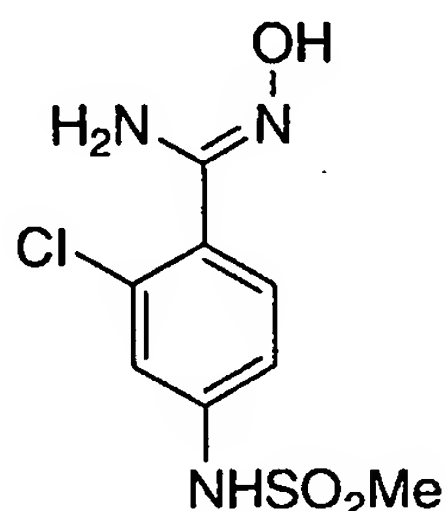
A 250 mL, round bottom flask was charged with 3.0 g (12.5 mmol) of 1-benzhydryl-3-fluoroazetidine and 80 mL of dichloromethane. To the stirring solution at -78 °C was added 4.6 mL (25 mmol) of [bis(2-methoxyethyl)amino]sulfur trifluoride via addition funnel over a period of about 3 h. The reaction mixture was allowed to warm slowly to ambient temperature overnight. The reaction mixture was added portionwise (with caution) to a large extractor containing water and saturated aqueous sodium bicarbonate solution. The mixture was extracted three times with 80 mL of dichloromethane. The combined organic layers were washed sequentially with saturated aqueous sodium bicarbonate solution, water and saturated aqueous brine, dried over sodium sulfate, and concentrated *in vacuo*. Purification by flash chromatography using a Biotage® system (gradient, hexane to 80 % ethyl acetate/hexane) afforded the desired product. LC/MS 242.1 (M+1).

Step B: 3-Fluoroazetidine trifluoroacetic acid salt

1-Benzhydryl-3-fluoroazetidine (1.7 g, 7.04 mmol) was dissolved in 60 mL of ethanol and 500 mg of 20% palladium hydroxide (dry basis) on carbon. The mixture was shaken under 40 psi

hydrogen for about 12 h. The mixture was filtered through a celite pad and the filter cake washed with 100 mL of methanol. The combined washings were treated with 10 mL of trifluoroacetic acid and concentrated to give two oils, the more dense of which is the desired fluoroazetidine salt. The mixture was not purified further. ¹H NMR (CDCl₃) δ 5.45-4.30 (dm, J = 56.7 Hz, 1 H), 4.46-4.38 (m, 2 H), 4.24-2.17 (m, 2 H).

INTERMEDIATE 6



2-Chloro-N'-hydroxy-4-[(methylsulfonyl)amino]benzenecarboximidamide

10 Step A: N-(3-Chloro-4-cyanophenyl)methanesulfonamide

To a stirred solution of 4-amino-2-chlorobenzonitrile (5.02 g, 32.9 mmol) in dichloromethane (80 mL) was added *N,N*-diisopropylethylamine (17.0 mL, 97.8 mmol) and methanesulfonyl chloride (3.0 mL, 38.8 mmol) at -78 °C. The reaction was then allowed to warm to room temperature slowly. After stirring at room temperature for 12 h, the reaction was quenched with 1

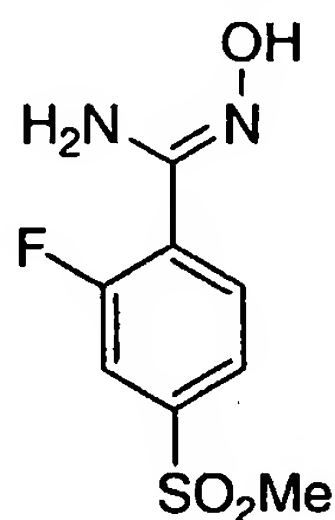
15 *N* hydrochloric acid. The organic phase was concentrated in vacuo and the residue was purified by flash chromatography (silica gel, 50:50 hexanes/ethyl acetate) to give the desired product.

Step B: 2-Chloro-N'-hydroxy-4-[(methylsulfonyl)amino]benzenecarboximidamide

To a stirred solution of the product from Step A (0.13 g, 0.565 mmol) in ethanol (3 mL) was added hydroxylamine (50% in water, 1.0 mL). The reaction was heated at 90 °C for 2 h. The

20 reaction was then concentrated to give the desired product.

INTERMEDIATE 7



2-Fluoro-N'-hydroxy-4-(methylsulfonyl)benzenecarboximidamideStep A: 2-Fluoro-1-methoxy-4-(methylthio)benzene

To a stirred solution of 4-bromo-2-fluoroanisole (5.0 g, 24.4 mmol) in THF (100 mL) was added *n*-butyllithium (23 mL, 1.6M in hexanes, 36.8 mmol) at -78 °C. After stirring at -78 °C for 1 h, dimethyl disulfide (11 mL, 12.2 mmol) was added and the reaction was then allowed to warm to room temperature slowly. After stirring at room temperature for 12 h, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo. The residue was used directly in next step.

10 Step B: 2-Fluoro-1-methoxy-4-(methylsulfonyl)benzene

To a stirred solution of the product from Step B (557 mg, 3.24 mmol) in dichloromethane (15 mL) was added *m*-chloroperbenzoic acid (2.19 g, 12.7 mmol). After stirring at room temperature for 2 h, the reaction was diluted with ethyl acetate. The organic phase was washed sequentially with 1 N aqueous sodium hydroxide solution and brine, and concentrated in vacuo. Purification by flash chromatography (silica gel, 75:25 hexanes/ethyl acetate) afforded the desired compound.

15 Step C: 2-Fluoro-4-(methylsulfonyl)phenol

To a stirred solution of the product from Step B (480 mg, 2.35 mmol) in dichloromethane (10 mL) was added boron tribromide (12.0 mL, 1.0 M in dichloromethane, 12.0 mmol) at -78 °C. The reaction was then allowed to warm to room temperature slowly. After stirring at room temperature for 12 h, the reaction was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, 50:50 hexanes/ethyl acetate) to give the desired compound.

20 Step D: 2-Fluoro-4-(methylsulfonyl)phenyl trifluoromethanesulfonate

To a stirred solution of the product from Step C (425 mg, 2.24 mmol) in pyridine (8 mL) was added trifluoromethanesulfonic anhydride (1.5 mL, 7.02 mmol) at 0 °C. After stirring at 0 °C for 3 h, the reaction was diluted with ethyl acetate and poured into 1N aqueous hydrochloric acid. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo. Purification by flash chromatography (50:50 hexanes/ethyl acetate) afforded the desired product.

25 Step E: 2-Fluoro-4-(methylsulfonyl)benzonitrile

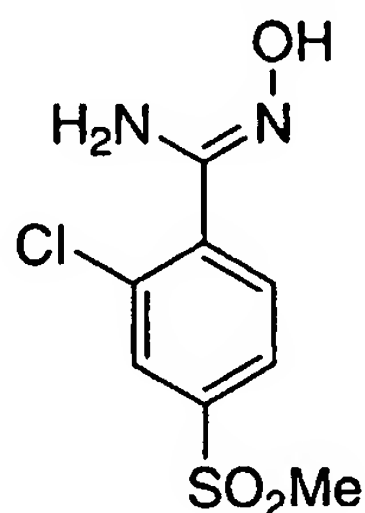
To a stirred solution of the product from Step D (662 mg, 2.06 mmol) in DMF (8 mL) was added zinc cyanide (951 mg, 8.1 mmol), and the reaction was then heated at 80 °C for 12 h. The reaction mixture was diluted with ethyl acetate and poured into brine. The organic phase was separated, and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo. Purification by flash chromatography (50:50 hexanes/ethyl acetate) afforded the desired product.

Step F: 2-Fluoro-N'-hydroxy-4-(methylsulfonyl)benzenecarboximidamide

To a stirred solution of the product from Step E (0.29 g, 0.144 mmol) in ethanol (15 mL) was added hydroxylamine (50% in water, 3.0 mL). The reaction was heated at 90 °C for 3 h. The reaction was then concentrated to give the desired product.

5

INTERMEDIATE 8



2-Chloro-4-methylsulphonyl-N'-hydroxybenzenecarboximidamide

Step A: 2-Chloro-4-(methylsulfonyl)benzamide

10 To 2-chloro-4-methylsulfonylbenzoic acid (20 g, 86 mmol) and *N*-hydroxysuccinimide (11.5 g, 100 mmol) in 300 mL of dichloromethane was added EDC (19.8 g, 100 mmol) and the resulting mixture was stirred at room temperature for 8 h. The mixture was then quenched with 100 mL of saturated aqueous sodium bicarbonate solution then diluted with 200 mL of water. The mixture was then extracted with ethyl acetate (3 x 300 mL), and the organic layers were washed with saturated aqueous sodium bicarbonate solution and saturated aqueous brine (100 mL each). The organic phase was dried over magnesium sulfate, filtered, and evaporated in vacuo to yield the crude ester. The ester was then dissolved into 200 mL of dioxane then treated with 100 mL of ammonium hydroxide. After stirring for 2 h, the reaction mixture was evaporated in vacuo, diluted with 700 mL of ethyl acetate and then washed with saturated aqueous brine (2 x 200 mL). The organic phase was then dried over magnesium sulfate, filtered, and evaporated in vacuo to yield the primary amide, which was used without further purification.

15

20

Step B: 2-Chloro-4-(methylsulfonyl)benzonitrile

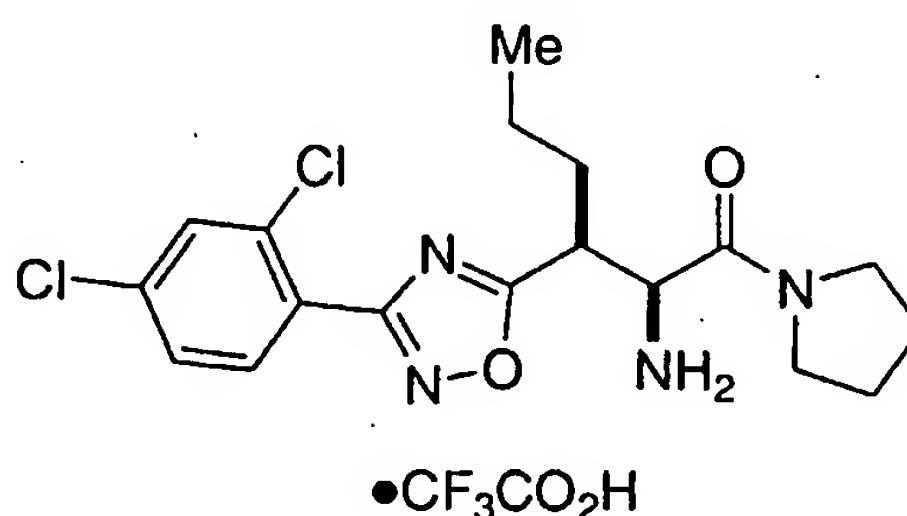
A portion of the primary amide from Step A (7.97 g, 34 mmol) in 80 mL of *N,N*-dimethylformamide was treated with cyanuric chloride (7.56 g, 41 mmol) and the solution was stirred at room temperature for 12 h. The mixture was then diluted with 400 mL of water and extracted with ethyl acetate (4 x 150 mL). The combined organic layers were then washed with 0.5 *N* aqueous sodium bicarbonate solution and saturated aqueous brine (2 x 100 mL each). The organic phase was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the crude nitrile, which was used without further purification.

25

Step C: 2-Chloro-4-methylsulphonyl-N'-hydroxybenzenecarboximidamide

The nitrile from Step B was dissolved into 100 mL of 1:1 ethanol/50% aqueous hydroxylamine then heated to reflux for 12 h. After evaporation of the solvent, the residue was dissolved into 400 mL of ethyl acetate then washed with saturated aqueous brine (150 mL). The organic phase was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the title compound, which was used without further purification. LC/MS 449.05 (M+1), 451.03 (M+3).

EXAMPLE 1



1-[(2S,3S)-2-Amino-3-[3-(2,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl]-1-oxohexyl]pyrrolidine, trifluoroacetic acid salt

10 Step A: Methyl (3S)-3-[(*tert*-butoxycarbonyl)amino]-4-oxo-4-pyrrolidin-1-ylbutanoate

To a stirred solution of *N*-BOC-L-aspartic acid β -methyl ester (15.1 g, 61.0 mmol) in DMF (50 mL) was added EDC (14.1 g, 73.7 mmol), HOBT (9.96 g, 73.7 mmol), pyrrolidine (10.2 mL, 122.4 mmol) and *N,N*-diisopropylethylamine (21.0 mL, 120.8 mmol). After stirring at room temperature for 12 h, the reaction was diluted with ethyl acetate. The organic phase was washed sequentially with 1N hydrochloric acid, 1N aqueous sodium hydroxide solution, and brine, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 50:50 hexanes/ethyl acetate) afforded the desired compound.

Step B: Methyl (2S)-2-[(1S)-1-[(*tert*-butoxycarbonyl)amino]-2-oxo-2-pyrrolidin-1-ylethyl]pent-4-enoate

20 To a stirred solution of the product from Step A (2.05 g, 6.83 mmol) in THF (30 mL) was added potassium hexamethyldisilazide (30.0 mL, 0.5M in toluene, 15.0 mmol) at -78°C . The resulting mixture was stirred at -78°C for 30 min. Allyl bromide (3.0 mL, 34.7 mmol) was then added. After stirring at -78°C for 2 h, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated *in vacuo*. Purification by flash chromatography (30:70 hexanes/ethyl acetate) afforded the desired product (major diastereoisomer from the reaction).

25 Step C: Methyl (2S)-2-[(1S)-1-[(*tert*-butoxycarbonyl)amino]-2-oxo-2-pyrrolidin-1-ylethyl]pentanoate

To a stirred solution of the product from Step B (1.54 g) in ethyl acetate (30 mL) was added 5% palladium on carbon (298 mg). The reaction mixture was stirred under hydrogen (1 atm) at room temperature for 2 h, then filtered through a pad of Celite and concentrated to give the desired product.

5 Step D: (2S)-2-[(1S)-1-[(*tert*-Butoxycarbonyl)amino]-2-oxo-2-pyrrolidin-1-ylethyl]pentanoic acid

To a stirred solution of the product from Step C (1.5 g) in THF (30 mL) and water (10 mL) was added lithium hydroxide (720 mg, 30.0 mmol). After stirring at room temperature for 12 h, the reaction was quenched with 1N hydrochloric acid. The organic phase was separated and the aqueous
10 phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo to give the desired product.

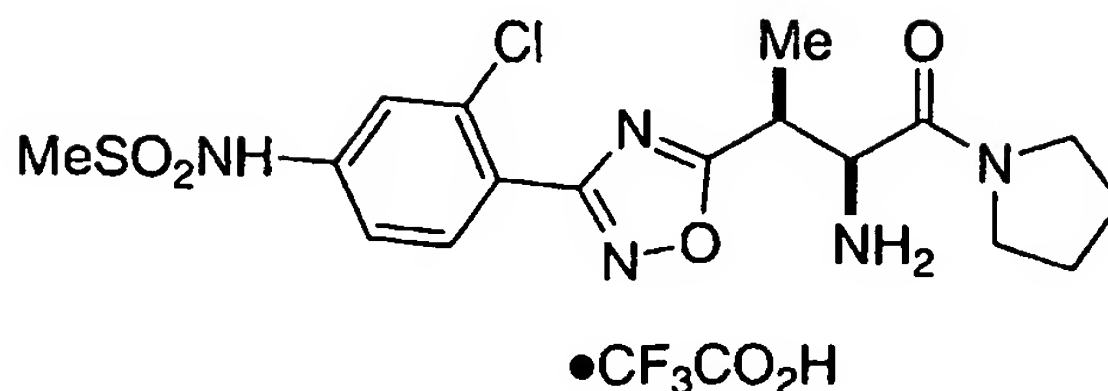
Step E: 1-[(2S,3S)-2-[(*tert*-Butoxycarbonyl)amino]-3-[3-(2,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl]-1-oxohexyl]pyrrolidine

To a stirred solution of the product from Step D (146.9 mg, 0.45 mmol) in
15 dichloromethane (5 mL) was added 1,1'-carbonyldiimidazole (157.6 mg, 0.97 mmol). After stirring at room temperature for 1 h, 2, 4-dichlorobenzamidoxime (318.8 mg, 1.56 mmol) was added. After stirring at room temperature for 2 h, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was then dissolved in 10 mL of toluene and heated at 110 °C for 12 h. The toluene was removed
20 under reduced pressure and the residue was then purified by preparative thin layer chromatography (silica gel, 50:50 hexanes/ethyl acetate) to give the desired product.

Step F: 1-[(2S,3S)-2-Amino-3-[3-(2,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl]-1-oxohexyl]pyrrolidine, trifluoroacetic acid salt

To a stirred solution of the product from Step E in 5 mL of dichloromethane was added 1
25 mL of trifluoroacetic acid. After 1 h at ambient temperature, the solution was concentrated in vacuo to give the desired product. LC/MS 398.9 (M+1).

EXAMPLE 2



1-[(2S,3S)-2-Amino-3-[3-[2-chloro-4-[(methylsulfonyl)amino]phenyl]-1,2,4-oxadiazol-5-yl]-1-oxobutyl]pyrrolidine, trifluoroacetic acid salt

5 Step A: Methyl (2S,3S)-3-[(tert-Butoxycarbonyl)amino]-2-methyl-4-oxo-4-pyrrolidin-1-ylbutanoate

To a stirred solution of the product from Example 1, Step A (2.2 g, 7.33 mmol) in THF (30 mL) was added lithium hexamethyldisilazide (16.0 mL, 1M in THF, 16.0 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 30 min. Iodomethane (2.8 mL, 45.0 mmol) was then added. After stirring at -78 °C for 2 h, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo. Purification by flash chromatography (30:70 hexanes/ethyl acetate) afforded the desired product (major diastereoisomer from the reaction).

15 Step B: (2S,3S)-3-[(tert-Butoxycarbonyl)amino]-2-methyl-4-oxo-4-pyrrolidin-1-ylbutanoic acid

To a stirred solution of the product from Step A (0.404 g, 1.29 mmol) in THF (30 mL) and water (10 mL) was added lithium hydroxide (96.0 mg, 4.0 mmol). After stirring at room temperature for 3 h, the reaction was quenched with 1N hydrochloric acid. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo to give the desired product.

20 Step C: 1-[(2S,3S)-2-[(tert-Butoxycarbonyl)amino]-3-[3-[2-chloro-4-[(methylsulfonyl)amino]phenyl]-1,2,4-oxadiazol-5-yl]-1-oxobutyl]pyrrolidine

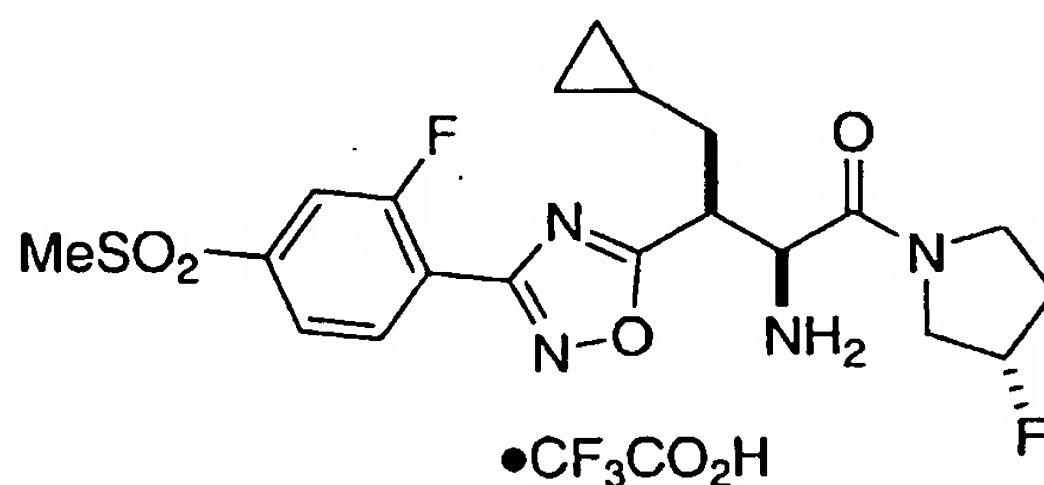
To a stirred solution of the product from Step B (132.0 mg, 0.44 mmol) in dichloromethane (5 mL) was added 1,1'-carbonyldiimidazole (148.0 mg, 0.91 mmol). After stirring at room temperature for 1 h, 2-chloro-N'-hydroxy-4-[(methylsulfonyl)amino] benzenecarboximidamide (Intermediate 6, 145.0 mg, 0.55 mmol) was added. After stirring at room temperature for 2 h, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic phase was then dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was dissolved in 10 mL of toluene and heated at 110 °C for 12 h. The toluene was removed under reduced pressure and the residue

was then purified by preparative thin layer chromatography (silica gel, 30:70 hexanes/ethyl acetate) to give the desired product.

Step D: 1-[(2*S*,3*S*)-2-Amino-3-[3-[2-chloro-4-[(methylsulfonyl)amino]phenyl]-1,2,4-oxadiazol-5-yl]-1-oxobutyl]pyrrolidine, trifluoroacetic acid salt

5 To a stirred solution of the product from Step C (7 mg) in 5 mL of dichloromethane was added 1 mL of trifluoroacetic acid. After 1 h at ambient temperature, the solution was concentrated in vacuo to give the desired product. LC/MS 430.2 (M+1).

EXAMPLE 3



(3*S*)-1-[(2*S*,3*S*)-2-Amino-4-cyclopropyl-3-[3-[2-fluoro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-1-oxobutyl]-3-fluoropyrrolidine, trifluoroacetic acid salt

Step A: Methyl (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-4-[(3*S*)-3-fluoropyrrolidin-1-yl]-4-oxobutanoate

15 To a stirred solution of *N*-BOC-L-aspartic acid β-methyl ester (10.04 g, 40.6 mmol) in DMF (50 mL) was added EDC (9.42 g, 49.1 mmol), HOBT (6.60 g, 48.9 mmol), (3*S*)-3-fluoropyrrolidine hydrochloride (Intermediate 1, 7.59 g, 60.7 mmol) and *N,N*-diisopropylethylamine (21.0 mL, 120.8 mmol). After stirring at room temperature for 12 h, the reaction was diluted with ethyl acetate. The organic phase was washed sequentially with 1*N* hydrochloric acid, 1*N* aqueous sodium hydroxide solution and brine, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 50:50 hexanes/ethyl acetate) afforded the desired compound.

Step B: Methyl (2*S*)-2-[(1*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-[(3*S*)-3-fluoropyrrolidin-1-yl]-2-oxoethyl]pent-4-enoate

25 To a stirred solution of the product from Step A (4.51 g, 14.2 mmol) in THF (150 mL) was added potassium hexamethyldisilazide (65.0 mL, 0.5*M* in toluene, 32.5.0 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 30 min. Allyl bromide (6.2 mL, 71.7 mmol) was then added. After stirring at -78 °C for 2 h, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo.

Purification by flash chromatography (30:70 hexanes/ethyl acetate) afforded the desired product (major diastereoisomer from the reaction).

Step C: (2S)-2-[(1S)-1-[(*tert*-Butoxycarbonyl)amino]-2-[(3S)-3-fluoropyrrolidin-1-yl]-2-oxoethyl]pent-4-enoic acid

5 To a stirred solution of the product from Step B (1.57 g, 4.358 mmol) in THF (30 mL) and water (20 mL) was added lithium hydroxide (1.2 g, 50.0 mmol). After stirring at room temperature for 12 h, the reaction was quenched with 1N hydrochloric acid. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with brine and concentrated in vacuo to give the desired product.

10 Step D: (3S)-1-[(2S,3S)-2-[(*tert*-Butoxycarbonyl)amino]-3-[3-[2-fluoro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-1-oxohex-5-en-1-yl]-3-fluoropyrrolidine
Essentially following the procedure described in Example 2, Step C, the title compound was prepared from the product of Step C and Intermediate 7.

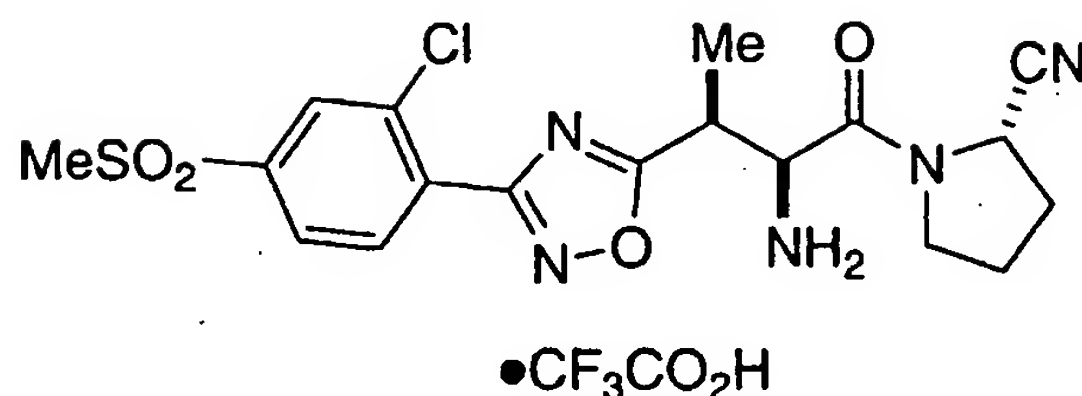
15 Step E: (3S)-1-[(2S,3S)-2-[(*tert*-Butoxycarbonyl)amino]-4-cyclopropyl-3-[3-[2-fluoro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-1-oxobutyl]-3-fluoropyrrolidine

20 To a stirred solution of the product from Step D (158 mg, 0.29 mmol) in ether (30 mL) was added diazomethane solution (40 mL, prepared from 2 g of *N*-methyl-*N*-nitrosourea) and palladium acetate (59.7 mg, 0.26 mmol) at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched with 1 mL of acetic acid. The solvent was removed under reduced pressure and the residue was purified by preparative thin layer chromatography (silica gel, 30:70 hexanes/ethyl acetate) to give the desired product.

Step F: (3S)-1-[(2S,3S)-2-Amino-4-cyclopropyl-3-[3-[2-fluoro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-1-oxobutyl]-3-fluoropyrrolidine, trifluoroacetic acid salt

25 To a stirred solution of the product from Step E (85 mg) in 5 mL of dichloromethane was added 1 mL of trifluoroacetic acid. After 1 h at ambient temperature, the solution was concentrated in vacuo to give the desired product. LC/MS 450.1 (M+1).

EXAMPLE 4



(2S)-1-[(2S,3S)-2-Amino-3-[3-[2-chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-1-oxobutyl]-2-cyanopyrrolidine, trifluoroacetic acid salt

5 Step A: 4-Benzyl 1-methyl (3S)-3-methyl-L-aspartate

BOC-L-aspartic acid 4-benzyl ester (20 g, 62 mmol) was dissolved in 300 mL of methanol and cooled to 0 °C. Trimethylsilyldiazomethane (130 mL, 260 mmol, 2M in hexanes) was added in portions until a yellow color persisted. After warming to room temperature, the solution was concentrated *in vacuo*. This crude material was dissolved in 225 mL of THF and added via cannula to a stirred solution of potassium bis(trimethylsilyl)amide (433 mL, 217 mmol, 0.5M in toluene) at -78 °C. Methyl iodide (13.5 mL, 217 mmol) was added to the mixture over 30 min and the resultant slurry was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with saturated aqueous brine, dried over sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using a Biotage® system (gradient, hexane to 30% ethyl acetate/hexane) afforded the desired product. LC/MS 374.2 (M + 23).

15 Step B: 1-Methyl (3S)-3-methyl-L-aspartate

The compound from Step A (7.3 g, 21 mmol) was dissolved in 60 mL of methanol and 0.8 g of 20% palladium hydroxide (dry basis) on carbon was added to the solution. The reaction flask was flushed with nitrogen and agitated under hydrogen (40 psi) for 3 h. The reaction mixture was then filtered through a Celite pad and washed with 100 mL of methanol. The combined filtrate and washings were concentrated *in vacuo* to afford the product which was used in the next step directly. LC/MS 284.0 (M+23).

25 Step C: Methyl (2S,3S)-2-[(tert-butylcarbonyl)amino]-3-[3-[2-chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]butanoate

To the crude acid from Step B (5.4 g, 21 mmol) in 150 mL of dichloromethane was added Intermediate 8 (6.1 g, 25 mmol) and EDC (7.9 g, 41 mmol). After stirring at room temperature for 12 h, the reaction was diluted with dichloromethane and the organic phase washed sequentially with two portions each of water and saturated aqueous brine solution, dried over sodium sulfate and evaporated *in*

vacuo to give the crude product which was purified by flash chromatography using a Biotage® system (gradient, 40% to 100% ethyl acetate/hexane). The pure material was next dissolved in 250 mL of toluene and the reaction mixture was heated to reflux for 48 h before it was cooled to room temperature. The solvent was removed *in vacuo* and the residue purified by flash chromatography using a Biotage® system (gradient, 20% to 80% ethyl acetate/hexane) to afford the pure product. LC/MS 374.0 (M+1-BOC).

Step D: (2S,3S)-2-[(*tert*-Butylcarbonyl)amino]-3-[3-[2-chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]butanoic acid

To a stirred solution of the ester from Step C (1 g, 2.11 mmol) in 50 mL of a 4:1 solution of tetrahydrofuran:water at 0 °C was added a solution of lithium hydroxide monohydrate (0.3 g, 6.33 mmol) in 8 mL of water. After stirring at 0 °C for 1 h, the THF was removed by evaporation under reduced pressure and 10 mL of 2N hydrochloric acid was added. The aqueous solution was extracted with three portions of ethyl acetate. The combined organic layers were washed with saturated aqueous brine, dried over sodium sulfate and concentrated *in vacuo* to afford the product which was used in the next step without purification. LC/MS 360.0 (M+1-BOC).

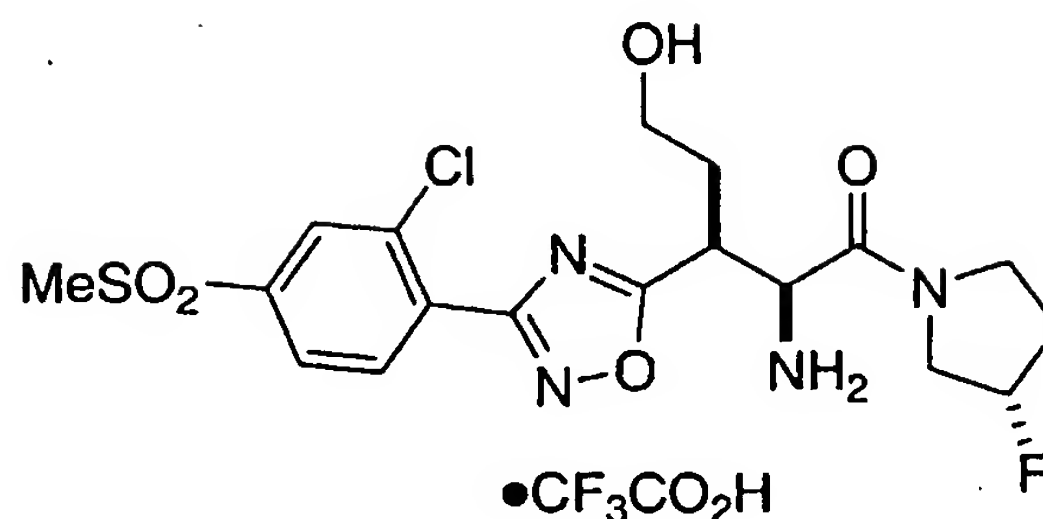
Step E: 1-((2S,3S)-2-[(*tert*-Butylcarbonyl)amino]-3-[3-[2-chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]butanoyl)-L-prolinamide

To the crude acid from Step D (0.15 g, 0.33 mmol) in 5 mL of dichloromethane was added L-prolineamide (0.057 g, 0.49 mmol), HOAt (0.090 g, 0.66 mmol), *N,N*-diisopropylethylamine (0.17 mL, 0.99 mmol) and HATU (0.25 g, 0.66 mmol). After stirring at room temperature for 12 h, the reaction was diluted with dichloromethane. The organic phase was washed sequentially with two portions of 0.5N aqueous sodium bicarbonate solution and saturated aqueous brine, dried over sodium sulfate, and evaporated *in vacuo*. Purification by HPLC (YMC Pro-C18 column, gradient elution, 10-90% acetonitrile/water with 0.1% TFA) afforded the title compound. LC/MS 556.2 (M+1).

Step F: (2S)-1-[(2S,3S)-2-Amino-3-[3-[2-chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-1-oxobutyl]-2-cyanopyrrolidine, trifluoroacetic acid salt

To a stirred solution of the coupled product from Step E (0.129 g, 0.23 mmol) in 2 mL of DMF was added cyanuric chloride (0.052 g, 0.28 mmol). After stirring at room temperature for 1 h, the reaction was diluted with ethyl acetate. The organic solution was washed sequentially with two portions of 0.5N aqueous sodium bicarbonate and saturated aqueous brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude material was dissolved in 4 mL of dichloromethane and 4 mL of trifluoroacetic acid. The reaction was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was purified by HPLC (YMC Pro-C18 column, gradient elution, 10-90% acetonitrile/water with 0.1% TFA) to afford the title product. LC/MS 438.0 (M+1).

EXAMPLE 5



(3S)-1-[(2S,3S)-2-Amino-3-[3-[2-chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-5-hydroxy-1-oxopentyl]-3-fluoropyrrolidine, trifluoroacetic acid salt

5 Step A: (3S)-1-[(2S)-2-[(*tert*-Butoxycarbonyl)amino]-3-[3-[2-Chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-1-oxohex-5-en-1-yl]-3-fluoropyrrolidine

To a solution of 2-[(1S)-1-[(*tert*-butoxycarbonyl)amino]-2-[(3S)-3-fluoropyrrolidin-1-yl]-2-oxoethyl]pent-4-enoic acid as a mixture of diastereomers (360 mg, 1.1 mmol), prepared as described in Example 3, Step C, in 11 mL of 10:1 dichloromethane/*N,N*-dimethylformamide was added Intermediate 8
 10 (572 mg, 2.3 mmol) and EDC (422 mg, 2.2 mmol). The resulting solution was stirred at room temperature for 48 h then concentrated and diluted with 100 mL of ethyl acetate. The resultant mixture was washed sequentially with 0.5N aqueous sodium bicarbonate solution and saturated aqueous brine (2 x 50 mL each). The organic phase was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the crude coupled product. This material was dissolved into 20 mL of toluene and 2 mL of *N,N*-
 15 dimethylformamide, then heated to 150 °C for 30 h. After evaporation of the toluene, the material was diluted with 100 mL of ethyl acetate then washed with saturated aqueous brine (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the crude product. This material was purified by preparative TLC (60% ethyl acetate/hexanes) to afford the pure product as a mixture of diastereomers. LC/MS 457.3 (M-Boc+1), 459.3 (M-Boc+3).

20 Step B: (4S)-4-[(*tert*-Butoxycarbonyl)amino]-3-[3-[2-chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-5-[(3S)-3-fluoropyrrolidin-1-yl]-5-oxopentanoic acid

To the product of Step A (221 mg, 0.4 mmol) in 50 mL of 4:1 *tert*-butanol/water was added potassium carbonate (69 mg, 0.4 mmol), sodium periodate (870 mg, 4.0 mmol), and potassium permanganate (8 mg, 0.05 mmol) and the resulting pink slurry was stirred at room temperature for 12 h.
 25 The mixture was then quenched with 10 mL of saturated aqueous sodium bisulfite solution then diluted with 80 mL of 1N hydrochloric acid. The mixture was then extracted with ethyl acetate (3 x 75 mL), and the organic layers were washed sequentially with 1N hydrochloric acid and saturated aqueous brine (2 x 50 mL each). The organic phase was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the crude acid, which was used without further purification. LC/MS 575.3 (M+1), 577.2 (M+3).

Step C: (3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-[3-[2-chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-5-[(3*S*)-3-fluoropyrrolidin-1-yl]-5-oxopentan-1-ol

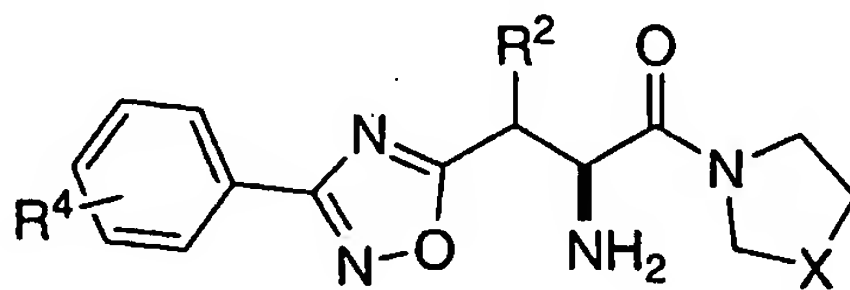
The acid from Step B in 50 mL of tetrahydrofuran at 0 °C was treated with *N,N*-diisopropylethylamine (0.13 mL, 0.8 mmol) and isobutyl chloroformate (0.1 mL, 0.8 mmol) then stirred at 0 °C. After 15 min, sodium borohydride (100 mg, 2.6 mmol) was added to the mixture followed by 10 mL of ethanol and the resulting solution bubbled vigorously. The mixture was allowed to warm to room temperature over 60 min, then diluted with 100 mL of 1*N* aqueous hydrochloric acid, then extracted with three 80-mL portions of ethyl acetate. The organic phases were combined and washed sequentially with 1*N* hydrochloric acid, saturated aqueous sodium bicarbonate solution, and saturated aqueous brine (80 mL each). The organic phase was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the crude alcohols. This material was purified by preparative TLC (5% methanol/dichloromethane) to give the pure alcohols as a mixture of (3*S*) and (3*R*) diastereomers. The diastereomeric mixture was resolved using a preparative chiral OD column (80% isopropanol/heptane) to give the desired (3*S*) diastereomer (least mobile under separation conditions). LC/MS 461.3 (*M*-*t*Bu+1), 463.2 (*M*-*t*Bu+3).

Step D: (3*S*)-1-[(2*S*,3*S*)-2-Amino-3-[3-[2-chloro-4-(methylsulfonyl)phenyl]-1,2,4-oxadiazol-5-yl]-5-hydroxy-1-oxopentyl]-3-fluoropyrrolidine, trifluoroacetic acid salt

The product from Step C (50 mg, 0.089 mmol) was dissolved into 10 mL of 1:1 trifluoroacetic acid/dichloromethane and stirred for 60 min then concentrated. The crude material was purified by reverse phase HPLC (YMC Pro-C18 column, gradient elution, 10 to 90% acetonitrile/water with 0.1% TFA) to afford the title compound as a colorless crystalline solid. LC/MS 461.3 (*M*+1), 463.2 (*M*+3).

Essentially following the procedures outlined for Examples 1-5, the Examples listed in Tables 1-3 were prepared.

TABLE 1

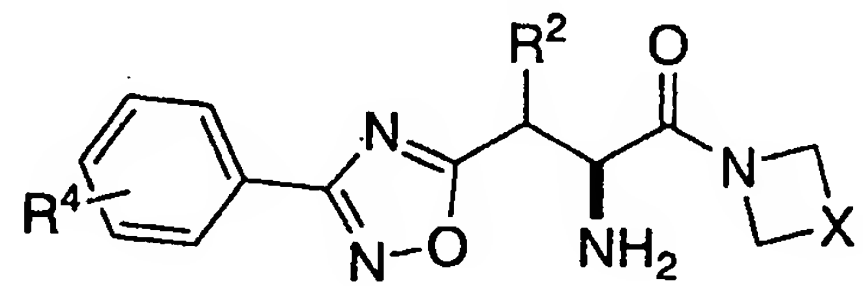


<u>Example</u>	<u>R⁴</u>	<u>R²</u>	<u>X</u>	<u>MS</u> <u>(M+1)</u>
6	2-Cl,4-Cl	Me	CH ₂	371.2

7	4-NHSO ₂ Me	Me	CH ₂	395.3
8	2-Cl	Me	CH ₂	337.1
9	2-Cl,4-Cl	Me	(S)-CHF	389.4
10	2-Cl,4-CF ₃	Me	CH ₂	405.2
11	2-Cl,4-F	Me	CH ₂	335.2
12	4-SO ₂ CF ₃	Me	CH ₂	434.2
13	2-Cl,4-SO ₂ Me	Me	CH ₂	414.9
14	2-Cl,4-SO ₂ Me	Me	(S)-CHF	433.1
15	2-Cl,4-NHSO ₂ Me	Me	(S)-CHF	447.9
16	2-Cl,4-NHSO ₂ Me	Me	(R)-CHF	448.1
17	4-SO ₂ NH ₂	<i>n</i> -Pr	CH ₂	409.1
18	2-F,4-CF ₃	Me	CH ₂	389.1
19	4-SO ₂ Me	<i>n</i> -Pr	CH ₂	408.1
20	2-Cl,4-NHSO ₂ Me	Me	CF ₂	466.0
21	4-SO ₂ Me	CH ₂ CHMe ₂	(S)-CHF	408.1
22	2-Cl,4-SO ₂ Me	CH ₂ CHMe ₂	(S)-CHF	475.0
23	4-SO ₂ Me	CH ₂ (<i>c</i> -Pr)	(S)-CHF	438.0
24	2-Cl,4-SO ₂ Me	CH ₂ (<i>c</i> -Pr)	(S)-CHF	473.1
25	2-Cl,4-Br	Me	S	432.9
26	4-NHSO ₂ Me	<i>n</i> -Pr	(S)-CHF	440.3

27	4-SO ₂ NH ₂	CH ₂ (c-Pr)	(S)-CHF	438.1
28	2-Cl,4-SO ₂ Me	CH ₂ CH=CH ₂	CH ₂	439.1
29	2-Cl,4-SO ₂ Me	CH ₂ CH=CH ₂	S	457.1
30	4-SO ₂ Me	CH ₂ (1-Me-c-Pr)	(S)-CHF	452.2
31	2-Me,4-SO ₂ Me	CH ₂ (c-Pr)	(S)-CHF	453.1
32	2-Cl,4-SO ₂ NH ₂	CH ₂ (c-Pr)	(S)-CHF	474.1
33	2-F,4-SO ₂ Me	CH ₂ (1-Me-c-Pr)	(S)-CHF	471.1
34	2-F,4-SO ₂ NH ₂	CH ₂ (c-Pr)	(S)-CHF	457.1
35	4-SO ₂ Me	CH ₂ CF ₂ Me	(S)-CHF	463.2
36	2-F,4-SO ₂ Me	CH ₂ (c-Pr)	CF ₂	473.1
37	2-F,4-SO ₂ Me	Me	CH ₂	381.0
38	4-SO ₂ Me	CH ₂ (c-Pr)	CH ₂	421.2
39	2-F,4-SO ₂ Me	CH ₂ (c-Pr)	CH ₂	438.1

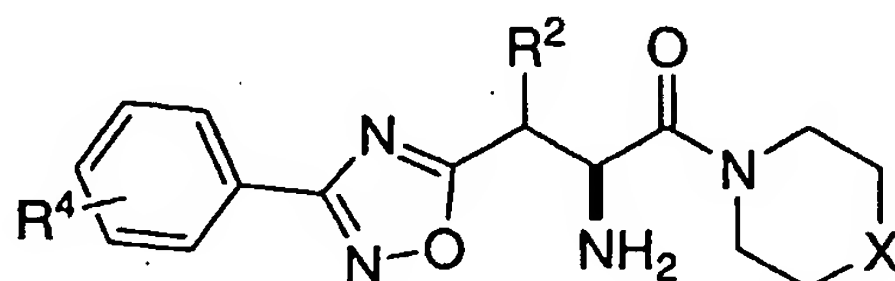
TABLE 2



<u>Example</u>	<u>R⁴</u>	<u>R²</u>	<u>X</u>	<u>MS (M+1)</u>
40	2-Cl,4-SO ₂ Me	Me	CH ₂	399.1

41	2-Cl,4-SO ₂ Me	Me	CF ₂	435.1
42	2-Cl,4-SO ₂ Me	Me	CHF	417.1

TABLE 3



<u>Example</u>	<u>R⁴</u>	<u>R²</u>	<u>X</u>	<u>MS</u> (M+1)
43	2-Cl,4-SO ₂ Me	Me	CH ₂	427.1
44	2-Cl,4-SO ₂ Me	Me	CHF	445.1
45	2-Cl,4-SO ₂ Me	Me	CF ₂	463.0

5 EXAMPLE OF A PHARMACEUTICAL FORMULATION

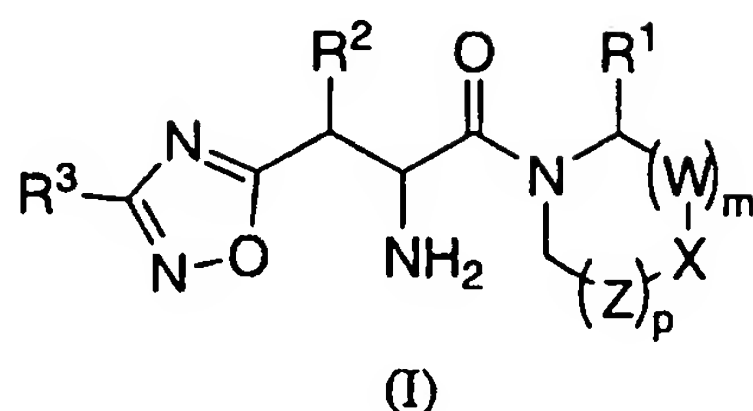
As a specific embodiment of an oral pharmaceutical composition, a 100 mg potency tablet is composed of 100 mg of any of the compounds of the present invention, 268 mg microcrystalline cellulose, 20 mg of croscarmellose sodium, and 4 mg of magnesium stearate. The active, microcrystalline cellulose, and croscarmellose are blended first. The mixture is then lubricated by magnesium stearate and pressed into tablets.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. The specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected

variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



- 5 or a pharmaceutically acceptable salt thereof; wherein
each n is independently 0, 1, or 2;
m and p are each independently 0 or 1;

X is CH₂, S, CHF, or CF₂;

- 10 W and Z are each independently CH₂, CHF, or CF₂;

R¹ is hydrogen or cyano;

R³ is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one to five R⁴ substituents;

15

R² is selected from the group consisting of

hydrogen,

C₁₋₁₀ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

20

C₂₋₁₀ alkenyl, wherein alkenyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

(CH₂)_n-aryl, wherein aryl is unsubstituted or substituted with one to five substituents

independently selected hydroxy, halogen, CO₂H, C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl,

and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to

25

five halogens,

(CH₂)_n-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three

substituents independently selected from hydroxy, halogen, CO₂H, C₁₋₆

alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are

unsubstituted or substituted with one to five halogens,

(CH₂)_n-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, CO₂H, C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

5 (CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, CO₂H, C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_nCOOH,

10 (CH₂)_nCOOC₁₋₆ alkyl,

(CH₂)_nCONR⁵R⁶, wherein R⁵ and R⁶ are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen and hydroxy and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

15 or wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

20 wherein any methylene (CH₂) carbon atom in R² is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens;

each R⁴ is independently selected from the group consisting of

30 halogen,
cyano,
hydroxy,
C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,
C₁₋₆ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,
(CH₂)_n-NR⁵R⁶,
35 (CH₂)_n-CONR⁵R⁶,

- (CH₂)_n-OCONR⁵R⁶,
 (CH₂)_n-SO₂NR⁵R⁶,
 (CH₂)_n-SO₂R⁸,
 (CH₂)_n-NR⁷SO₂R⁸,
 5 (CH₂)_n-NR⁷CONR⁵R⁶,
 (CH₂)_n-NR⁷COR⁷,
 (CH₂)_n-NR⁷CO₂R⁸,
 (CH₂)_n-COOH,
 (CH₂)_n-COOC₁₋₆ alkyl,
 10 (CH₂)_n-aryl, wherein aryl is unsubstituted or substituted with one to five substituents
 independently selected from halogen, hydroxy, CO₂H,
 C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ alkoxy, wherein alkyl and
 alkoxy are unsubstituted or substituted with one to five halogens,
 (CH₂)_n-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three
 15 substituents independently selected from hydroxy, halogen, CO₂H, C₁₋₆
 alkyloxycarbonyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ alkoxy, wherein alkyl and
 alkoxy are unsubstituted or substituted with one to five halogens,
 (CH₂)_n-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three
 substituents independently selected from oxo, hydroxy, halogen, CO₂H, C₁₋₆
 20 alkyloxycarbonyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ alkoxy, wherein alkyl and
 alkoxy are unsubstituted or substituted with one to five halogens,
 (CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three
 substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy,
 wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,
 25 wherein any methylene (CH₂) carbon atom in R⁴ is unsubstituted or substituted with one to two
 groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or
 substituted with one to five halogens;

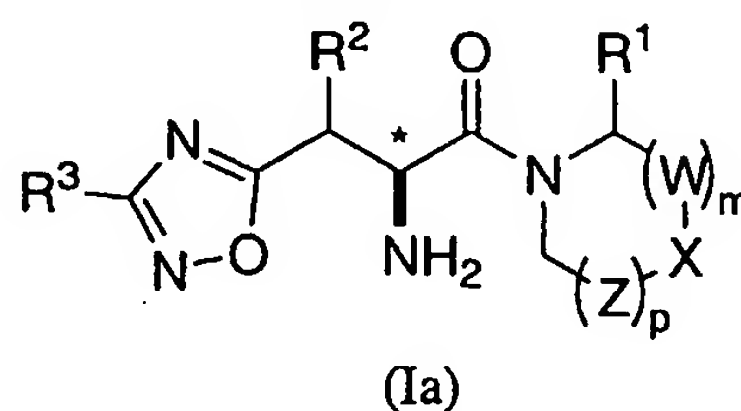
- R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl,
 30 (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted
 with one to five substituents independently selected from halogen and hydroxy and wherein phenyl and
 cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from
 halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted
 with one to five halogens;

or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

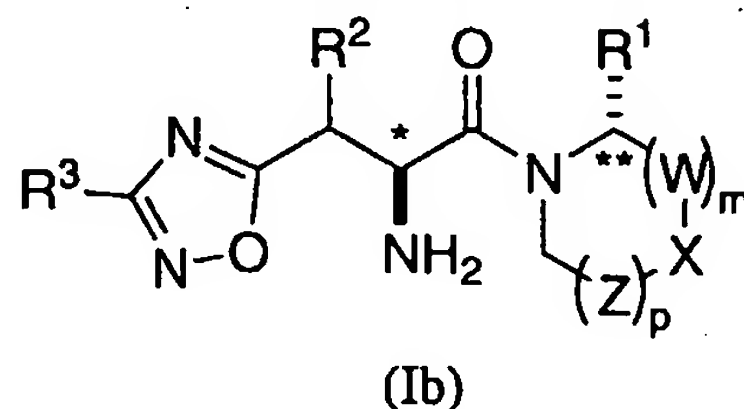
each R⁸ is independently selected from the group consisting of tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens, and wherein any methylene (CH₂) carbon atom in R⁸ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens; and

each R⁷ is hydrogen or R⁸.

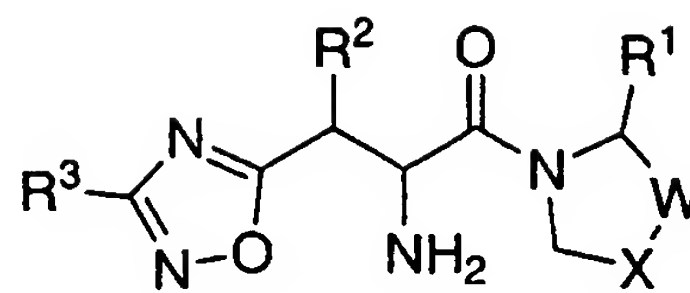
2. The compound of Claim 1 wherein the carbon atom marked with an * has the stereochemical configuration as depicted in formula Ia:



3. The compound of Claim 2 wherein the carbon atom attached to R¹ marked with an ** has the stereochemical configuration as depicted in the formula Ib:

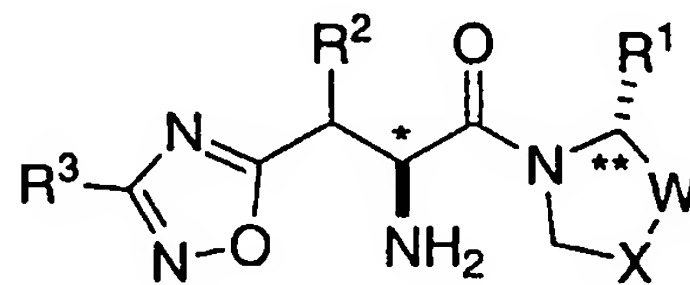


4. The compound of Claim 1 wherein m is 1 and p is 0 as depicted in formula Ic:



(Ic)

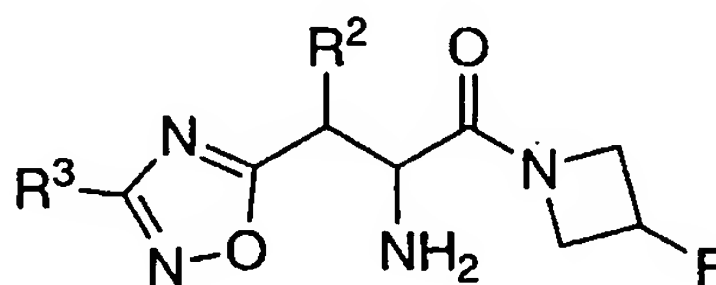
5. The compound of Claim 4 wherein the carbon atom marked with an * and the carbon atom marked with an ** have the stereochemical configurations as depicted in the formula Id:



(Id)

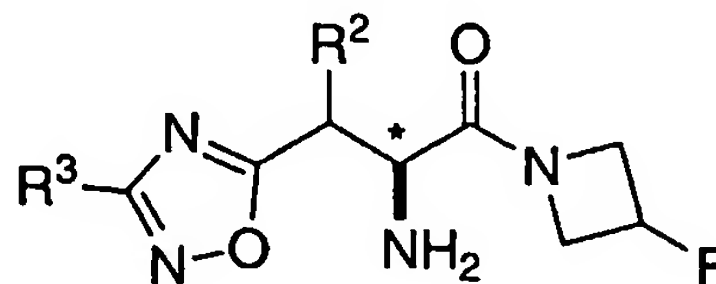
5 6. The compound of Claim 5 wherein R¹ is hydrogen; W is CH₂; and X is CH₂, CHF or CF₂.

7. The compound of Claim 1 wherein R¹ is hydrogen, X is CHF, and m and p are 0 as depicted in the formula Ie:



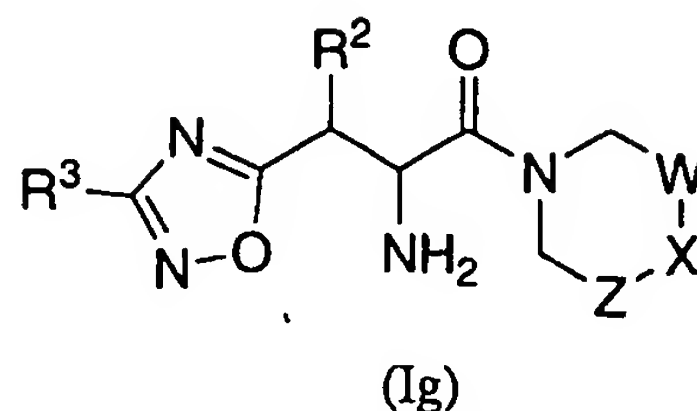
(Ie)

8. The compound of Claim 7 wherein the carbon atom marked with an * has the stereochemical configuration as depicted in the formula If:

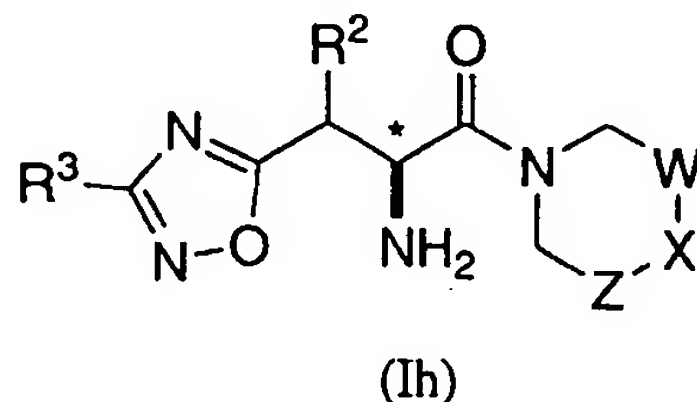


(If)

9. The compound of Claim 1 wherein R^1 is hydrogen, and m and p are 1 as depicted in formula Ig:



10. The compound of Claim 9 wherein the carbon atom marked with an * has the stereochemical configuration as depicted in the formula Ih:



11. The compound of Claim 10 wherein W and Z are CH_2 and X is CHF or CF_2 .

12. The compound of Claim 1 wherein R^2 is selected from the group consisting of :
 C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents
 independently selected from halogen or hydroxy,
 C₂₋₆ alkenyl, wherein alkenyl is unsubstituted or substituted with one to five substituents
 independently selected from halogen or hydroxy,
 (CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three
 substituents independently selected from halogen, hydroxy, CO₂H, C₁₋₆
 alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are
 unsubstituted or substituted with one to five halogens,
 (CH₂)_nCOOH,
 (CH₂)_nCOOC₁₋₆ alkyl,
 (CH₂)_nCONR⁵R⁶, wherein R⁵ and R⁶ are independently selected from the group consisting of
 hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl,
 wherein alkyl is unsubstituted or substituted with one to five substituents independently
 selected from halogen and hydroxy and wherein phenyl and cycloalkyl are unsubstituted
 or substituted with one to five substituents independently selected from halogen,

hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;
or wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and
5 morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy,
wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and
wherein any methylene (CH₂) carbon atom in R² is unsubstituted or substituted with one to two
groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted
10 with one to five halogens.

13. The compound of Claim 12 wherein R² is selected from the group consisting of :
C₁₋₃ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

15 CH₂-C₃₋₆ cycloalkyl,

COOH,

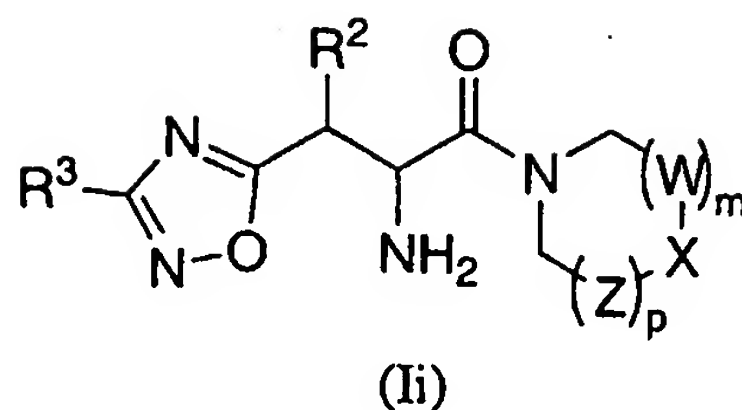
COOC₁₋₆ alkyl,

CONR⁵R⁶, wherein R⁵ and R⁶ are independently selected from the group consisting of
hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl,

20 wherein alkyl is unsubstituted or substituted with one to five substituents independently
selected from halogen and hydroxy and wherein phenyl and cycloalkyl are unsubstituted
or substituted with one to five substituents independently selected from halogen,
hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or
substituted with one to five halogens;

25 or wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocyclic
ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said
heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected
from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or
substituted with one to five halogens.

30 14. The compound of Claim 1 of structural formula Ii:



wherein X is CH₂, S, CHF, or CF₂;

W and Z are each independently CH₂, CHF, or CF₂;

R³ is aryl, unsubstituted or substituted with one to three R⁴ substituents;

5 R² is selected from the group consisting of:

methyl,

ethyl,

propyl,

2-methylpropyl,

10 propenyl,

CH₂-cyclopropyl,

CH₂-(1-methylcyclopropyl),

2-hydroxyethyl, and

2,2-difluoropropyl; and

15 each R⁴ is independently selected from the group consisting of:

halogen,

C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens;

C₁₋₆ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,

SO₂NR⁵R⁶,

20 SO₂R⁸,

NR⁷SO₂R⁸, and

heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents independently selected from hydroxy, halogen, CO₂H,

25 C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

15. The compound of Claim 14 wherein R³ is selected from the group consisting of:

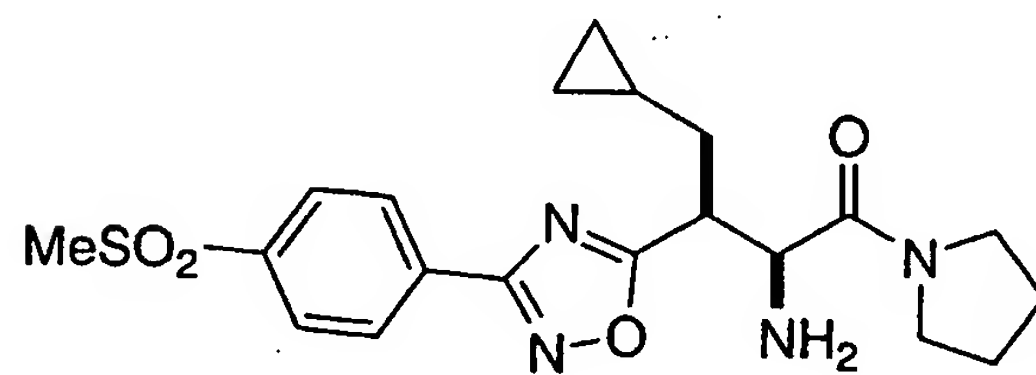
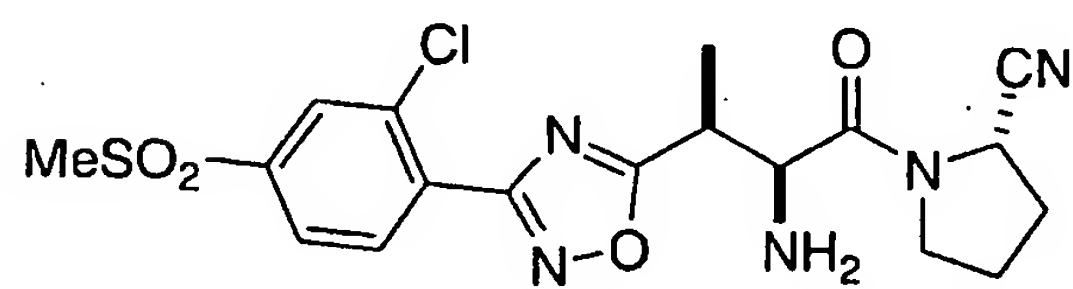
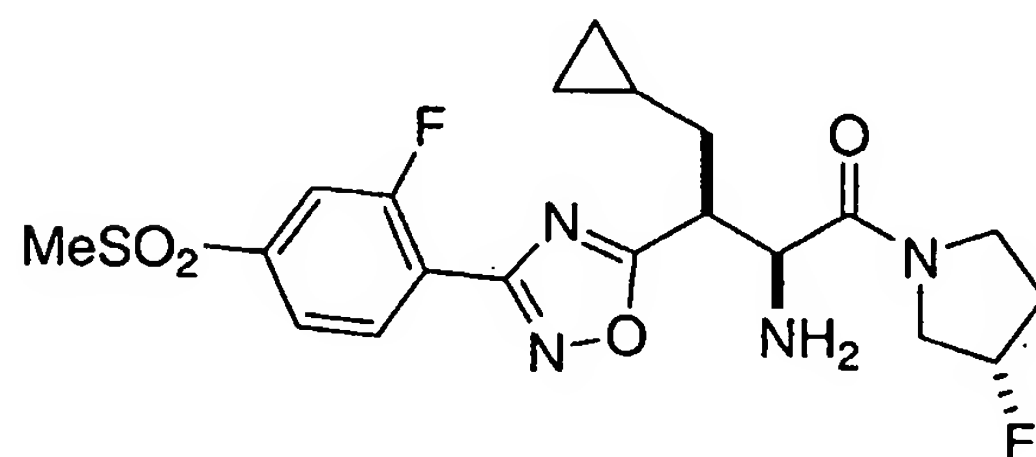
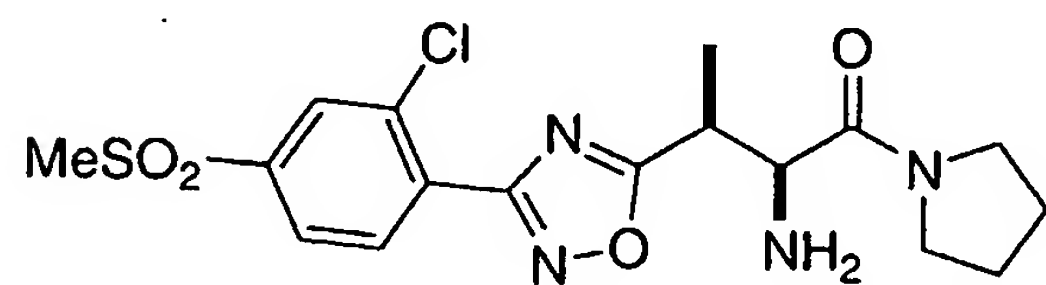
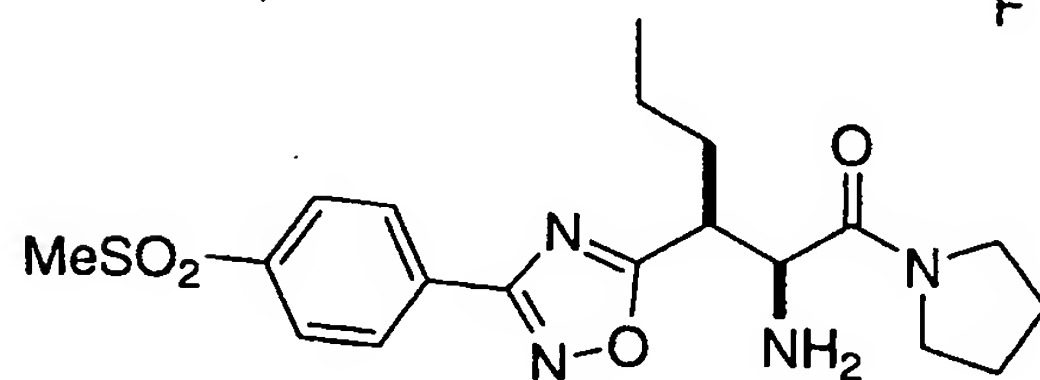
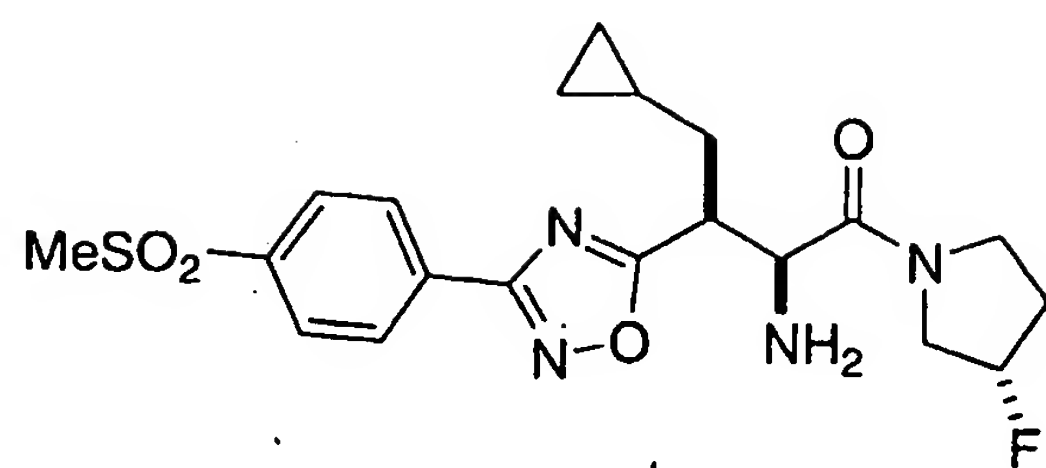
2-(trifluoromethoxy)phenyl,

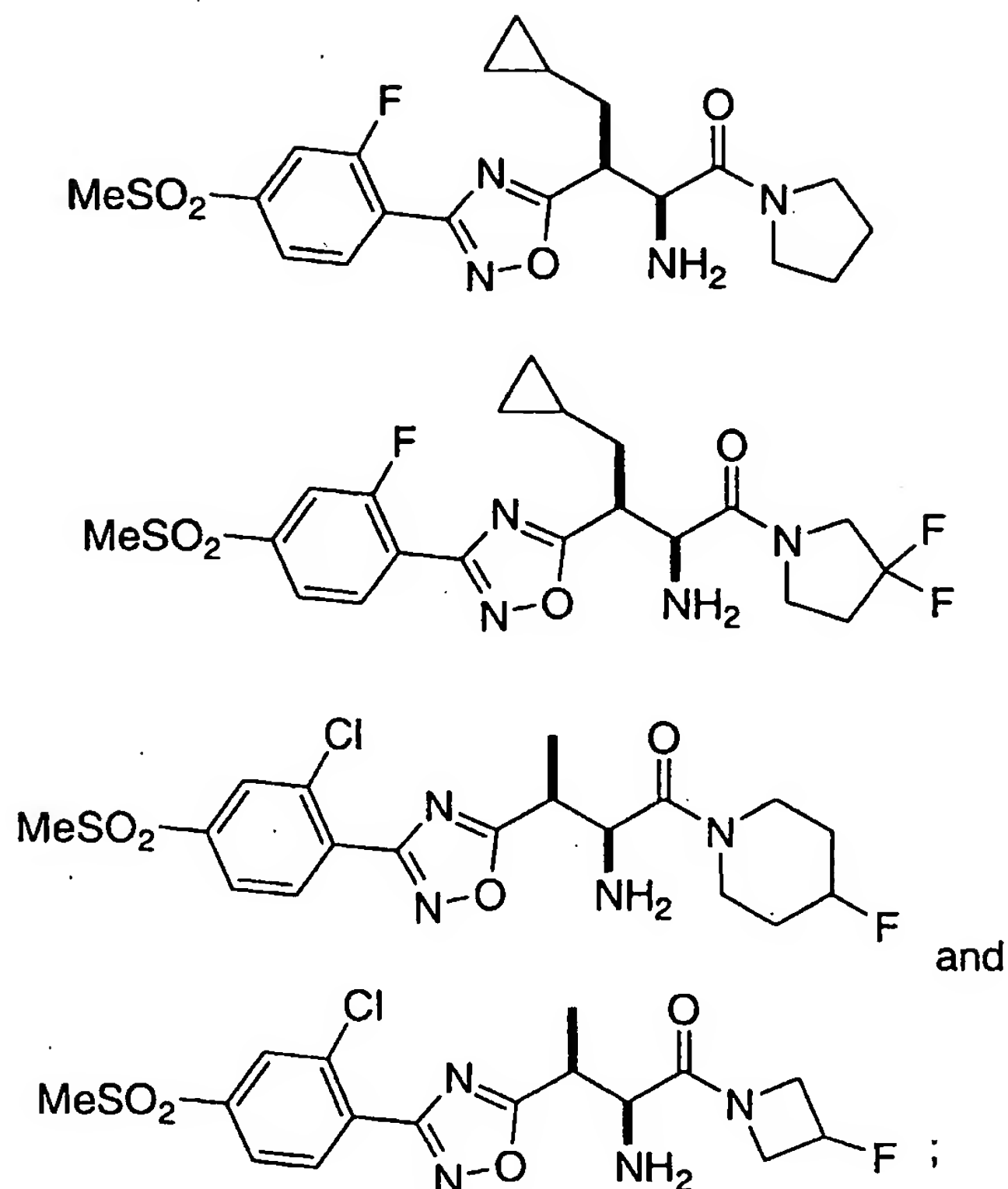
4-(trifluoromethoxy)phenyl,

30 3,5-dichlorophenyl,

2,4-dichlorophenyl,
2,4-difluorophenyl,
3,5-difluorophenyl,
2-fluorophenyl,
5 4-fluorophenyl,
2-chlorophenyl,
4-chlorophenyl,
2-(trifluoromethyl)phenyl,
3-(trifluoromethyl)phenyl,
10 4-(trifluoromethyl)phenyl,
2-fluoro-4-(trifluoromethyl)phenyl,
2-chloro-4-(trifluoromethyl)phenyl,
2,6-dichloro-4-(trifluoromethyl)phenyl,
2-chloro-4-fluorophenyl,
15 2-chloro-4-bromophenyl,
4-(methylsulfonyl)phenyl,
4-[(trifluoromethyl)sulfonyl]phenyl,
4-(aminosulfonyl)phenyl,
4-[cyclopropylamino)sulfonyl]phenyl,
20 4-[(methylsulfonyl)amino]phenyl,
2-fluoro-4-(methylsulfonyl)phenyl,
2-chloro-4-(methylsulfonyl)phenyl,
2-fluoro-4-[(methylsulfonyl)amino]phenyl,
2-chloro-4-[(methylsulfonyl)amino]phenyl,
25 2-fluoro-4-(aminosulfonyl)phenyl,
2-chloro-4-(aminosulfonyl)phenyl,
2-chloro-4-(tetrazol-1-yl)phenyl, and
2-chloro-4-(tetrazol-5-yl)phenyl.

30 16. The compound of Claim 1 which is selected from the group consisting of:





or a pharmaceutically acceptable salt thereof.

5 17. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

10 18. Use of a compound in accordance with Claim 1 in the manufacture of a medicament for use in treating a condition selected from the group consisting of hyperglycemia, Type 2 diabetes, obesity, and a lipid disorder in a mammal.

19. The use according to Claim 18 wherein said lipid disorder is selected from the group consisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, and high LDL.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/15133

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C 07D 271/06, 413/06, 417/06; A 61K 31/382, 31/397, 31/4025, 31/4245, 31/445, 31/541
US CL : 548/131; 546/209; 544/60; 514/210.18, 227.8, 326, 364

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/131; 546/209; 544/60; 514/210.18, 227.8, 326, 364

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOUSSEBOIS, C., et al., "27. Synthèse de deux nouveaux acides aminés phénoliques comportant un cycle 1,2,4-oxadiazole," [Synthesis of two new phenolic amino acids containing the 1,2,4-oxadiazole ring], Helvetica Chimica Acta, vol. 60(1), pages 237-242 (Jan. 1977) at p. 242, lines 12 - 21 (example 8) ("alpha-Amino-beta-[3-(p-benzyloxyphenyl)-1,2,4-oxadiazol-5-yl]-N-(2-methoxyethyl)propionamide").	4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 16
A	CALDWELL, C.G., et al., "Fluoropyrrolidine amides as dipeptidyl peptidase IV inhibitors," Bioorg. Med. Chem. Lett., vol. 14(5), pages 1265-1268 (March 8, 2004), at p. 1265, col. 2, lines 5 - 11 (compounds 3, 5 and 6); p. 1267, col. 1, Table 2 (compounds 24 - 27).	4 - 13, 16
A	226th AMERICAN CHEMICAL SOCIETY MEETING, New York, New York, U.S.A. (September 9, 2003), Division of Medicinal Chemistry (Abstracts only), Tuesday evening Poster session: especially Poster 90 (FUKUSHIMA, H., et al., "DPP-IV Inhibitors (2): Synthesis and Evaluation of Novel 2-Cyano-4-Fluoropyrrolidines," compound 1); and Poster 92 (ASHTON, W., et al., "Diastereoselective Synthesis and Configuration-Dependent Activity of (3-Substituted-Cycloalkyl)Glycine Pyrrolidides as DPP-IV Inhibitors").	4 - 13, 16

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 July 2005 (18.07.2005)

Date of mailing of the international search report

17 AUG 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-8300

Authorized officer

Anthony J. Paviglian

Telephone No. (571) 272-3107

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/15133

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE1 097 998 (ANGELINI, F.) 26 January 1961 (26.01.1961), at col. 5, line 14 (Example 16).	4 - 13, 16
A	MALAMAS, M.S., et al., "Antihyperglycemic activity of new 1,2,4-oxadiazolidine-3,5-diones," Eur. J. Med. Chem., vol. 36(1), pages 31 - 42 (Jan. 2001), at p. 35, col. 1, lines 22 - 39 (Table III), especially compounds 50 and 51.	4 - 13, 16
A, P	U.S. 6,861,440 B2 (BOEHRINGER, et al.) 01 March 2005 (01.03.2005), especially at col. 90 (Example 177); see also col. 88 (Example 172) and col. 89 (Examples 173, 174, 175, 176 and 178).	4 - 13, 16
A, P	U.S. 2004/0138274 A1 (DACK, et al.) 15 July 2004 (15.07.2004), at p. 32, lines 22 - 25 ("(2S)-2-tert-butoxycarbonylamino-3-(3-phenyl-[1,2,4]oxadiazol-5-yl)propionic acid benzyl ester"); p. 44, line 3 ("Example 90"); p. 35, lines 1 - 4 ("(2S)-2-Amino-3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propionic acid methyl ester"); and p. 38, lines 10 - 13 ("(2S)-2-Amino-3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-propionic acid benzyl ester trifluoroacetate").	4 - 13, 16
A, P	EDMONDSON, S.D., et al., "Potent and selective proline derived dipeptidyl peptidase IV inhibitors," Bioorg. Med. Chem. Lett., vol. 14(20), pages 5151-5155 (Oct. 2004), at p. 5151, col. 2, lines 13, Figure 1 (compound 4); and at p. 5153, col. 2, lines 23 - 26 & Table 5 (compounds 47 - 50).	4 - 13, 16
A, P	XU, J., et al., "Discovery of potent and selective phenylalanine based dipeptidyl peptidase IV inhibitors," Bioorg. Med. Chem. Lett., vol. 15(10), pages 2533-2536 (16 May 2005)(available online 9 April 2005), at page 2533, col. 2, Figure 1, compound 2; and p. 2535, col. 1, Table 2, compound 32.	4 - 13, 16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/15133

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1 - 3, 14, 15 and 17 - 19
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/15133

Continuation of Box II Reason 2:

The numerous variables (e.g., W, X, Z, m, p, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸), and their voluminous, complex meanings and innumerable permutations and combinations make it impossible to determine the full scope and complete meaning of the claimed subject matter in Claims 1, 2, 3, 14, 15, 17, 18 and 19. In particular, the heterocyclic ring containing variables (W)_m, X, and (Z)_p, may vary from a four-membered ring to a six membered ring, with or without an additional sulfur atom in the ring; in addition, variables R² and R³ may be any aryl or heteroaryl without limitation as to ring size or identity of heteroatoms, if any. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and, as such, the listed claims do not comply with the requirements of PCT Article 6. Therefore it is not possible to perform a meaningful search on Claims 1, 2, 3, 14, 15, 17, 18 and 19. A search of the art will be performed for the other claims.

Continuation of B. FIELDS SEARCHED Item 3:

CAS Online - STN search of structure in CAPLUS and BEILSTEIN; DERWENT and EAST (U.S. Patent Literature) search terms: 1,2,4-oxadiazole; 3-phenyl; amino acid; pyrrolidine; piperidine; thiomorpholine.